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THROMBOSIS OF THE DEEP VEINS OF THE LEG

ITS CLINICAL SIGNIFICANCE AS EXEMPLIFIED IN THREE HUNDRED AND FIFTY-ONE AUTOPSIES

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Generally accepted facts are not invariably supported by published data. The voluminous literature on venous thrombosis contains surprisingly little pertaining to the deep veins of the calf. This is scarcely attributable to ignorance or to a lack of appreciation of phlebothrombosis in this part of the body. Experienced necroscopists have long been aware that the legs constitute a common, though often clinically silent, reservoir of clot formation during life and at autopsy seek here when other more readily accessible sources of embolism have failed. Rather, it appears to us that such factors as antagonism on the part of embalmers toward extensive dissection, restrictions imposed by relatives and ambiguity or possible interpretations of the laws pertaining to mutilation may be more potent reasons for the paucity of figures with respect to this part of the body.

Much credit for the recognition of the common occurrence and the clinical importance of venous thrombosis in the calf of the leg belongs to Jakob Erdheim of Vienna. Not a prolific writer, Erdheim seems to have confined his observations on this particular subject to his lectures and demonstrations. Even so, his emphatic insistence that the veins of

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the leg constitute a most important source of pulmonary emboli made an indelible impression on listeners,[1] and by them the information has been passed on to many others.

A survey of the literature indicates that only Rössle,[2] Neumann [3] and Frykholm [4] have accumulated any considerable data bearing directly upon the postmortem incidence of thrombosis of the veins of the calf. More extended reference to the work of these men will be found in the comment in the present communication.

MATERIAL AND METHODS

Prompted by a desire for firsthand knowledge and with the feeling that easily accessible statistics in English might be appreciated by others, we routinely removed the soleus and gastrocnemius muscles from as many as possible of an unselected group of patients, both adolescents and adults, on whom autopsies were performed over a period beginning with March 1939 and extending well into February of the following year. In order to ascertain whether venous thrombosis was more frequent in one type of hospital than in another, cooperative effort was resorted to, and material was accumulated from (1) a charity hospital, (2) a state psychopathic institution and (3) two private hospitals.

Removal of the muscles was accomplished through a lateral incision extending from the ankle to above the knee; we carefully dissected the muscles from the posterior aspect of the leg bones and were certain to detach high enough to catch the heads of the gastrocnemius muscle and as much of the popliteal vein as possible. The specimens, properly labeled, were fixed by suspension in large crocks of solution of formaldehyde and then sectioned transversely at intervals of approximately 2 cm. The frequent variations in color and consistency of the clots often made necessary the taking of several blocks at different levels along the muscles and from various veins. Identification as to source was carried through to the microscopic sections. Individual macroscopic descriptions were made in all instances. Specimens exhibiting empty veins or containing only fluid blood were not studied microscopically. On this basis 209 pairs of muscles were subjected to microstudy, with the result that thrombi of varying age proved to be present in 52.7 per cent of the whole group of 351 patients (table 1).

While we were cognizant of Neumann's [3] observations concerning the frequency of thrombi in the plantar veins, it was deemed inadvisable, except in a very few instances, to go any farther than the legs for fear of losing the good will of the embalmers. For the same reason we did not attempt to dissect the veins of the thigh; so our observations of the femoral veins were of necessity confined to the part accessible from the abdomen. On the other hand, a conscious effort was made throughout to search carefully for venous thrombi in all parts of the body ordinarily examined at autopsy.

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1. Osgood, E. E.: Personal communication to the authors, 1928. Menne, F. R.: Personal communication to the authors, 1931.

2. Rössle, R.: Ueber die Bedeutung und die Entstehung der Wadenvenenthrombosen, Virchows Arch. f. path. Anat. **300**:180, 1937.

3. Neumann, R.: Ursprungszentren und Entwicklungsformen der Bein-Thrombose, Virchows Arch. f. path. Anat. **301**:708, 1938.

4. Frykholm, R.: Pathogenesis in Venous Thrombosis and Mechanical Prophylaxis, Nord. med. (Hygiea) **4**:3534, 1939.

TABLE 1.—*Summary of Data on Autopsies of Three Hundred and Fifty-One Unselected Patients*

	Hospital				
	MCH*	SV†	WS‡	PS§	Total
Total number of autopsies	200	61	55	35	351
Number of patients with thrombosis of leg veins (thrombus subgroup)	118	30	23	14	185
Percentage of occurrence of thrombosis	59%	49%	41.8%	40%	52.7%
Total number of patients with fatal pulmonary emboli	7	4	0	0	11
With fatal emboli from leg veins alone	4	1	0	0	5
With fatal emboli possibly from other than leg veins	2	2	0	0	4
With fatal emboli not from leg veins	1	1	0	0	2
Percentage of deaths in whole group	3.5%	6.5%	....	....	3.13%
Percentage of deaths in thrombus subgroup	5.09%	10.0%	....	....	4.8%
Deaths of medical patients	4	2	0	0	6
Deaths of surgical patients	3	2	0	0	5
Males with fatal pulmonary emboli	5	4	0	0	9
Females with fatal pulmonary emboli	2	0	0	0	2
Total number of patients with nonfatal emboli	24	3	7	6	40
With infarction	5	2	1	2	10
Without infarction	19	1	6	4	30
Percentage of patients with nonfatal emboli in whole group	12%	4.9%	12.7%	17.1%	11.39%
Percentage of patients with nonfatal emboli in thrombosis subgroup	20.3%	9.67%	30.4%	42.8%	20.5%
Males with nonfatal pulmonary emboli	12	3	5	0	20
Females with nonfatal pulmonary emboli	12	0	2	6	20
Percentage of patients with pulmonary emboli in whole group	15.5%	11.4%	12.7%	17.1%	14.55%
Total number of patients with thrombi occurring elsewhere	22	8	10	2	42
In thrombus subgroup with thrombi elsewhere	19	5	6	2	32
Not included in thrombus subgroup	3	3	4	1	11
Service classification					
Number of surgical patients in whole group	29	12	2	9	52
Number of medical patients in whole group	159	45	52	26	280
Number of patients in both surgical and medical or in undetermined services in whole group	12	6	1	0	19
Number of surgical patients in thrombus subgroup	16	3	1	4	24
Number of medical patients in thrombus subgroup	95	22	22	10	149
Number of patients in both surgical and medical or in undetermined services in thrombus subgroup	7	5	1	0	13
Percentage of surgical patients with thrombi in leg veins	55.2%	25.0%	50.0%	44.4%	46.9%
Percentage of medical patients with thrombi in leg veins	59.7%	51.1%	42.3%	38.4%	53.2%
Percentage of patients in both surgical and medical or in undetermined services with thrombi in leg veins	58.3%	83.3%	100%	....	68.4%
Sex classification					
Number of males in whole group	131	43	38	12	224
Number of females in whole group	69	18	17	23	127
Percentage of males in thrombus subgroup	60.3%	46.5%	39.4%	25.0%	52.2%
Percentage of females in thrombus subgroup	56.5%	55.5%	47.0%	47.8%	53.5%
Incidental findings					
Number of patients with edema in whole group	73	9	11	10	103
Number of patients with edema in thrombus subgroup	48	8	8	6	70
Number of patients with muscle atrophy in whole group	71	19	23	9	122
Number of patients with muscle atrophy in thrombus subgroup	46	16	11	5	78
Number of patients with phlebitis in whole group	9	2	4	2	17
Number of muscles studied microscopically	151	30	9	19	209
Percentage of occurrence of phlebitis in muscles sectioned	5.9%	6.6%	13.8%	10.5%	8.1%
Age grouping					
Oldest patient with thrombosis of leg veins	94	86	92	84	94
Youngest patient with thrombosis of leg veins	15	30	27	46	15
Average age of patients with thrombosis of leg veins	65.4	59.9	69.9	67.5	64.9
Oldest patient in whole group	94	86	92	84	94
Youngest patient in whole group	15	15	27	29	15
Average age of patients in whole group	60.8	55.8	65.9	57.6	59.78

* MCH, Multnomah County Hospital, Portland.
† SV, St. Vincent's Hospital, Portland.
‡ WS, Western State Hospital, Washington.
§ PS, Portland Sanitarium and Hospital, Portland.

For a time the circumference of the calves was measured, but the procedure was later abandoned, for the reason that the legs had not been measured when the patients first took to bed and there was therefore no basis for comparison. Furthermore, it was found that the size of the two legs was likely to be the same even when there was unilateral thrombosis.

GENERAL CONSIDERATIONS

To one unfamiliar with the anatomy of the muscles of the calf it is a distinct surprise to observe the number and size of their veins. Often the posterior tibial and peroneal arteries are paralleled by three or four venae comitantes. Within the substance of the muscles veins are plentiful and if distended stand out strikingly in cross sections. Likewise, the small but numerous venae surales of the heads of the gastrocnemius muscle are readily seen when filled with blood. Not uncommonly veins along the arteries and in the soleus muscle attain a diameter of 10 or even 15 mm. Sclerosis is infrequent; so empty veins collapse readily and give an erroneous impression of being normally small. Occasional valves are demonstrable in the major veins. Tributaries to large veins usually enter at a right angle.

After a little experience one has no difficulty in distinguishing between fresh thrombi and postmortem clots. Since the propagated part of a thrombus and a postmortem clot may look alike, it is essential that one follow such clots serially by means of transverse cuts. Frequently the character will change to that of an unmistakable thrombus caudal to where the clot is first encountered. Often an apparently unchanged and even empty vein of large caliber will show one or more tributaries occluded by thrombi whose ends protrude for a little way into the lumen of the parent vessel. It is difficult to escape the conviction that such unsupported clots are not a prolific source of small emboli. Another variation of progressive thrombosis in the direction of the heart is a gradual inward-building of the clot from the periphery, leaving an opening at the middle. Apparently organization of thrombi in the deep veins of the leg proceeds rather slowly and haltingly, since one often has the experience of seeing segments several centimeters long literally pop out of freshly transected veins without one's having exerted any appreciable pressure on the muscle. Unless this fact is appreciated, whole thrombi may be lost or discarded as of no importance.

As a rule, if thrombi exist at all more than one vein will be involved and the process will be bilateral. The veins accompanying the larger arteries and those within the soleus muscle are much more often occluded than are those of the gastrocnemius muscle, the ratio in our series being about 2 to 1 (table 2). Almost any portion of the soleus muscle may be the seat of thrombi, but in the gastrocnemius muscle the clots are likely

to be limited to the heads of the muscle or the area near the insertion of the achilles tendon. There is a slight predilection for the right side in unilateral thrombosis (table 2).

TABLE 2.—*Location and Number of Thrombosed Leg Veins*

	Multnomah County Hospital	St. Vincent's Hospital	Western State (Wash.)	Portland Sanitarium and Hospital	Totals
Bilateral	69	20	10	11	110
Unilateral	49*	10	13	3	75
Right soleus muscle	95	24	12	14	145
Left soleus muscle	87	26	12	11	136
Right gastrocnemius muscle	36	10	12	3	61
Left gastrocnemius muscle	36	10	6	3	55

* Among the 118 patients with thrombosis were 7 in whom one leg had been amputated. Thus it is possible that unilateral involvement is higher than might have been the case had both legs been present.

TABLE 3.—*Pertinent Data on Eleven Instances of Fatal Pulmonary Embolism*

Sex	Age	Primary Condition of Patient	Medical	Surgical	Location of Pulmonary Emboli	Source of Pulmonary Emboli	State of Deep Veins of Leg	Days in Bed
M	89	Infection of hand; infarction, lower lobe of left lung	..	+	Both main branches	Leg veins alone	Thrombosis, right leg only	22
M	85	Old coronary thrombosis and infarction with aneurysm; congestive heart failure	+	..	Either main branch	Leg veins alone	Thrombosis, bilateral	25
M	67	Carcinoma of rectum, resected; fecal fistula	..	+	Both main branches	Leg veins alone	Thrombosis, bilateral	16
M	51	Coronary thrombosis; infarction, left ventricle	+	..	Main branches	Leg veins alone	Thrombosis, bilateral	123
M	64	Bilateral inguinal hernia; herniorrhaphy	..	+	Main artery and both branches	Left femoral, iliac or leg veins	Thrombosis, left leg only	15
M	64	Prostatic hyperplasia with obstruction; pyelonephritis	+	..	Both main branches	Leg veins alone	Thrombosis, left leg only	2
F	51	Recent hysterectomy; thrombosis of pelvic veins	..	+	Main artery and both branches	Iliac veins, inferior vena cava or leg veins	Thrombosis, bilateral	13
M	73	Thrombophlebitis, right iliac, femoral and superficial veins	+	..	Main artery and both branches	One or more of involved veins	Thrombosis, bilateral	6
F	71	Carcinomatosis; marked coronary arteriosclerosis	+	..	Main artery	Veins of broad ligaments	No thrombi	3
M	34	Recent gastric resection	..	+	Main artery	Left internal iliac vein	No thrombi	13
M	70	Thyrotoxic heart with congestive heart failure	+	..	Right main branch	Right atrium or leg veins	Thrombosis, left leg only	13
M, 9 F, 2	..	.....	6 54.5%	5 45.5%	From leg veins, 5, 45.4% Likely not from leg veins, 4, 36.3% Not from leg veins, 2, 18.2%			

In a large series one may rightly anticipate the finding of thrombi of all ages, but in our experience the great majority were either fresh or in the stage of softening and early organization, and their age tended to

parallel the length of time in bed. Only occasionally will canalized thrombi alone exist, and in such cases reference to the clinical record will sometimes elicit the information that the patient has had a prior confinement. Ancient thrombi are easily recognized macroscopically either by a rusty brown color or by a form of fenestration that is different from the diffuse sievelike openings in canalized arteries. The openings are always situated at the periphery around an almost solid, white, central plug, in a fashion simulating a spoked wheel. The size of the channels is surprisingly great. In some instances the degree of thrombus formation is minimal; perhaps it is limited to one small vein or, in the case of larger vessels, to the sinuses behind the valves. In the latter instance, when the thrombi organize the valves become fixed and functionless in the same manner as those Edwards and Edwards [5] produced experimentally.

ANALYSIS OF FINDINGS

Although the essential data have been put in tabular form, certain features deserve amplification.

Age.—Both the youngest, 15 years, and the oldest, 94 years, of the patients displayed thrombosis. The average age of the whole group was 59.78 years; for the 185 persons in whom occlusion was found in a leg vein the average age was 64.9 years. The difference is not impressive.

Sex.—The ratio of nearly 2 males to 1 female is a chance figure, yet one which from year to year tends to remain fairly constant, probably because it seems to be easier to obtain permission for autopsy on males. The frequency of thrombosis was practically the same—52.2 per cent in males and 53.5 per cent in females.

Service Classification.—Of all the patients, 79.7 per cent were medically treated, and 14.8 per cent were surgically treated; a third category, termed "mixed," was required to classify 5.4 per cent of the patients suffering from both medical and surgical conditions and treated accordingly. As between the strictly medical and surgical patients there was little difference in the incidence of thrombosis, for of the former 53.2 per cent and of the latter 46.9 per cent had demonstrable thrombi in the veins of the calf. In the "mixed" category the incidence of thrombosis was significantly higher, amounting to 68.4 per cent.

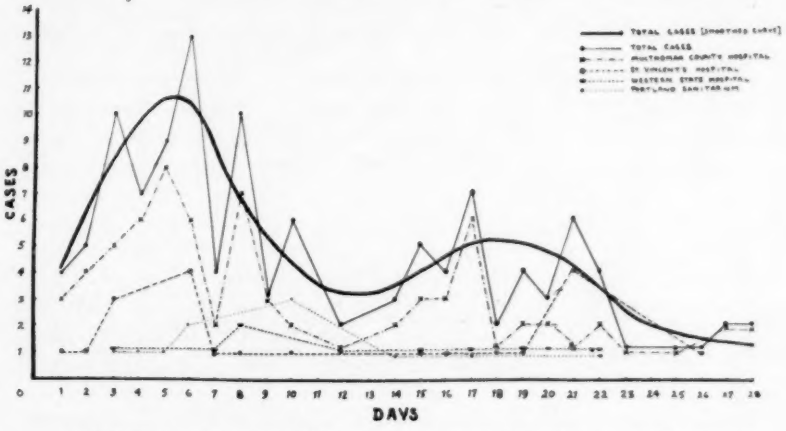
Time in Bed.—As might be anticipated for a group of this size in which the patients came from widely different types of hospitals, the period of recumbency ranged from one day (a single patient suffering from severe burns) to seven years (1 patient). However, as shown in

5. Edwards, E. A., and Edwards, J. E.: The Effect of Thrombophlebitis on the Venous Valve, Surg., Gynec. & Obst. **65**:310, 1937.

the combined curve (chart 1), the great majority of deaths occurred within four weeks after admission and the curve had two peaks, one during the fifth and sixth days and one during the third week. It should be emphasized that all of the 351 patients were almost continuously bedridden from the time of entry to death.

Fatal Pulmonary Embolism.—Eleven, 3.13 per cent, of the entire group died as a direct result of pulmonary embolism. Of these, 6 were medical patients and 5 were surgical patients; 9 were male and the other 2 were female, or, putting it differently, 4.01 per cent of all males died from pulmonary embolism, in contrast to 1.57 per cent of all females.

If the veins of the thigh and the plantar veins, which we could not examine, are left out of consideration, it would appear that among the



As indicated by the composite curve, the greatest number of deaths among persons found to have thrombosed leg veins occurred during the last half of the first and in the third week in the hospital.

11 fatalities from embolism, the most probable point of origin was from thrombi in the veins of the calf in 5 instances (45.4 per cent). The pulmonary emboli found were of such diameter, length and age as to mirror those still remaining in the legs. Multiple emboli were far more common than single massive clots. There were 4 instances (36.3 per cent) in which the lethal emboli could have come from thrombosed leg veins, but the presence of other thrombi either in large veins nearer the heart or within its right chambers seemed to be more likely sources. In only 2 of the 11 there were no thrombi in the leg veins; in 1 of these the emboli came from the veins of the broad ligaments and in the other from an internal iliac vessel. Circulatory failure on a cardiac basis was present in 4 of the 6 medical patients but was not a factor in the deaths of the surgical patients. Computed on the 185 instances of phlebothrom-

bosis of the legs, 4.8 per cent of the deaths in this subgroup were due to pulmonary embolism.

Nonfatal Pulmonary Embolism.—This condition was found in 40 patients. In 10 of these the emboli occluded branches large enough to bring about infarction; in the remainder they were either too small or of too recent origin to have caused necrosis. Some were discovered only by opening the smaller pulmonary branches according to the German technic recently reemphasized by Belt.[6] It is interesting to note that, although 11.39 per cent of all patients examined showed nonfatal emboli, the figure almost doubles (20.5 per cent) in the subgroup of 185 patients

TABLE 4.—*List of the Venous Thrombi, Exclusive of Those in the Deep Veins of the Leg, Occurring in Three Hundred and Fifty-One Unselected Necropsies*

Periurethral vein	1
Periurethral vein and saphenous parva	1
Periprostatic vein	7
Periprostatic vein and right atrium	2
Periprostatic vein and inferior vena cava	1
Periprostatic vein, inferior vena cava, left iliac vein	1
Veins of the broad ligaments	3
Veins of the broad ligaments and varicose veins of the leg	1
Iliac veins	2
Inferior vena cava	2
Portal vein	2
Renal vein	1
Right atrium, right ventricle or both	5
Varicose veins of legs	3
Popliteal vein	1
Popliteal and posterior veins of thighs	1
Saphenous parva, left	2
Superficial veins about an ulcer of the leg	1
Femoral vein (in aneurysm only)	1
Plantar veins	1
Pulmonary arteries (primary thrombosis)	2
Thyroid veins (post-thyroidectomy)	1
Cavernous sinus	1
Total	43

whose leg veins were thrombosed. Smaller emboli were discovered in 20 males and in an equal number of females, although on a percentage basis, since males outnumbered females about 2:1, small emboli proved almost twice as common in females (15.7 per cent) as in males (8.9 per cent). This is diametrically opposed to what took place with fatal embolism. If cases both of fatal and of nonfatal embolism are added together, the total incidence of pulmonary embolism becomes 14.55 per cent.

Other Thrombi.—A total of 32 patients displayed thrombosis in parts of the body in addition to the leg veins; 11 others showed no involvement of the veins of the calf but harbored clots in other locations. It would thus appear that when venous thrombosis occurs there is a strong probability that the deep vessels of the leg will be one of the sites. The several locations of thrombi outside the legs are listed in table 4.

6. Belt, T. H.: Demonstration of Small Pulmonary Emboli at Autopsy, J. Tech. Methods **15**:39, 1936.

Phlebitis.—There has long been a tendency to speak of phlebothrombosis and phlebitis as synonymous states. This, we feel, is a mistake. During the process of resorption of a clot one not infrequently observes monocytes and lymphocytes along with blood pigment within the walls of the vein. There can be no doubt that the function of the monocytes is to engulf the blood pigment. While the purpose of the lymphocytes is not clear, we doubt that they represent an inflammatory reaction, or if so, they represent a secondary phenomenon and bear no causal relationship to thrombus formation. The diagnosis of acute phlebitis is hazardous in the absence of polymorphonuclear leukocytes. Among the 209 specimens from which blocks of the leg muscles were studied histologically, phlebitis was discovered only 17 times (8.1 per cent), and even this small figure becomes less significant when the details of individual instances are given. Thus, in a patient with carcinoma of the sigmoid flexure of the colon and peritonitis the left femoral vein but not the veins of the legs revealed inflammation; a patient suffering from pulmonary and intestinal tuberculosis had phlebitis of one femoral vein only; in the same category was a man with osteomyelitis and phlebitis of one common iliac vein; a fourth patient, dying from congestive heart failure, exhibited inflammation of a superficial varicose vein of the leg, while the deep vessels escaped. If these patients are eliminated, the occurrence of phlebitis involving the veins of the calf amounts to only 6.2 per cent, and in 2 of the remaining 13 patients no thrombi were present. In 1, the process was focal and minimal in that only part of the circumference of a single vein was involved; in the other, a woman dying of subacute bacterial endocarditis, there was nothing more than an extension from the popliteal artery which had become blocked by a septic embolus, probably through the medium of the communicating vessels recently described by Winternitz and Le Compte.[7] The vein was not occluded. Among those with phlebitis of the veins of the calf were a patient who died of generalized peritonitis complicating a ruptured appendix, in whom only the outer part of the vein wall was affected, and a patient with a fracture of the femur, in whom the femoral vein and the veins of the calf on the injured side were the seat of phlebitis. Six times acute or subacute inflammation was concurrent with thrombosis of the leg veins, but always the process was either focal or slight, and the clots at this level were bland. Two examples of phlebitis were quite different from the others. One occurred in a woman who had streptococcic cellulitis of the thigh for which she was put to bed for fifty-two days and in whom the veins of the soleus muscles were both thrombosed and inflamed. The other was seen in a 73 year old man who had a primary phlebitis of the right

7. Winternitz, M. C., and Le Compte, P. M.: Experimental Infectious Angiitis, Am. J. Path. **16**:1, 1940.

iliac, femoral and superficial veins for which he had been in bed six days. Phlebitis was marked on the affected side, and the leg veins were occluded. Our experience leads to the conclusion that so far as the veins of the calf are concerned phlebitis has little to do with thrombus formation.

Edema.—Altogether, 103 patients with edema affecting the legs alone or with generalized edema were encountered, a percentage of 29.3. Among these were 70 (37.3 per cent) in whom the deep vessels of the calf were blocked by thrombi. It is doubtful if edema per se bears any relation to phlebothrombosis, since it is only a little more frequent among

TABLE 5.—*Clinical Grouping of Cases*

Clinical Service and Group	MCH*	SV†	WS‡	PS§	Total
Cardiovascular					
In whole group	83	17	19	11	130
In thrombus subgroup	48	9	7	5	69
Percentage with thrombosis	57.7	52.9	36.8	45.4	53.07
Infection					
In whole group	55	14	17	13	99
In thrombus subgroup	32	7	10	4	53
Percentage with thrombosis	58.18	50.0	58.8	30.7	52.5
Cachexia					
In whole group	34	17	8	6	65
In thrombus subgroup	22	8	2	5	37
Percentage with thrombosis	64.7	47.06	25.0	83.3	56.9
Obstructions					
In whole group	10	3	2	0	15
In thrombus subgroup	5	0	1	0	6
Percentage with thrombosis	50.0	....	50.0	....	40.0
Miscellaneous					
In whole group	18	9	9	5	41
In thrombus subgroup	11	6	3	0	20

* MCH, Multnomah County Hospital, Portland.
† SV, St. Vincent's Hospital, Portland.
‡ WS, Western State Hospital, Washington.
§ PS, Portland Sanitarium and Hospital, Portland.

persons with involvement of the veins in the leg than in those without thrombosis there. In most instances the edema could be ascribed to cardiac weakness.

Atrophy of Leg Muscles.—The possibility that atony or atrophy might predispose to thrombosis in a situation where adequate venous function depends on muscular activity as well as on gravity led us to note the gross and microscopic state of the muscle fibers. Atrophy was demonstrable in 122 patients (34.7 per cent) out of the whole group; 78 of these (63.9 per cent) had thrombosed leg veins, a difference of 29.2 per cent. Since the material was seen only at autopsy the factor of atony could not be evaluated.

Clinical Grouping.—With the hope of ascertaining whether clot formation in the leg veins was more frequent in one clinical condition than

in another, an attempt was made to segregate the cases of these patients according to the major conditions found. All too often there was troublesome overlapping, and we were forced to catalogue 41 cases as "miscellaneous." Perhaps a better designation would be "mixed." The figures obtained have been included for what they may be worth (table 5). Leaving this miscellaneous category out of consideration, we were surprised to learn that venous thrombosis in the calf occurs almost equally commonly among persons with cardiovascular diseases, infections or cachexias. In the obstructive category were the cases of 15 patients suffering from hyperplasia of the prostate gland or lesions of the bowel, uncomplicated by infection or cachexia, 40 per cent of whom had phlebothrombosis. Again we would emphasize that the one factor common to all, with or without thrombosis, was continuous rest in bed for varying periods of time without the benefit of planned and systematic exercise.

COMMENT

Presumably to test the validity of clinical evidence of frequent thrombosis of the plantar veins and the deep veins of the legs, Rössle,[2] in 1937, dissected the legs and thighs of 324 persons over 20 years of age who came to necropsy. Of these, 88 (27.1 per cent) harbored thrombi in the veins of the calf. Concomitant thrombosis in the femoral vein and the veins of the calf was found 38 times; on the other hand, there were only 7 instances of involvement of the femoral or hypogastric veins in the absence of thrombosed leg veins. Rössle raised the question as to whether the leg veins can be the source of pulmonary emboli, as occasionally happens in like-sized vessels, such as the pelvic veins. It was his feeling that emboli originating from the leg veins rarely become fatal but are nevertheless significant in that they tend to extend on into the femoral and iliac veins, from which the fulminating emboli originate. Even so, in carefully dissected preparations Rössle observed 3 instances in which massive pulmonary obstruction could be accounted for only on the basis of antemortem clots located in the veins of the calf. Frequently associated with the thrombosis were degenerative and atrophic changes in the leg muscles, and for this association Rössle offered three possible explanations: (1) that the alterations are due to thrombosis, against which is the fact that the clots are usually more recent than the changes in the muscles; (2) that degeneration of the muscles leads to the formation of substances causing clotting, and (3) that the two processes are independent, although perhaps the result of a common cause.

Voegt[8] further investigated Rössle's material, paying especial attention to the effects of long confinement in bed. The calf muscles and the

8. Voegt, H.: Veränderungen der Wadenmuskulatur bei Venenthrombose und langem Frankenlager, Virchows Arch. f. path. Anat. **300**:190, 1937.

rectus abdominis and biceps muscles from the same subjects were compared histologically. Five persons with thrombosed leg veins showed degenerative phenomena and atrophy of the muscles, but 22 others, likewise bedridden for a long time, had equally severe alterations of the leg muscles in the absence of thrombosis. The control muscles are described as "negative." Pressure, circulatory disturbances and inactivity were felt to be responsible for the changes in the muscles. Voegt suggested that degenerating muscle may liberate thrombogenic substances leading to terminal thrombosis.

In 1938 Neumann [8] reported his observations on a series of 165 consecutive autopsies in which the venous system was widely and thoroughly searched for thrombi. Special attention was paid to the veins of the lower extremities, and the report is based mainly on these findings. The series included autopsies on 84 females and 81 males, aged 17 to 88 years. In the 100 subjects showing thrombosis of the lower extremities the localization was: plantar region, 71 per cent; internal malleolar region, 17 per cent; leg, 87 per cent, and thigh, 22 per cent. Never was thrombosis limited to the thigh. Neumann attached great importance to the fact that the malleolar vessels, connecting the feet and legs, were so seldom involved even when both the plantar and the leg vessels contained thrombi. This seems to be the basis for his conclusion that there must be two centers of origin for venous clotting in the lower extremities, namely, the plantar and the leg region. The veins of the calf were much more often affected alone (29 per cent) than were the plantar veins (12 per cent). Also the more frequent combinations of occluded veins, leaving out of consideration the malleolar canal vessels, placed the veins of the calf far ahead of all others. The most common combination proved to be bilateral involvement of the veins of the calf and the foot. Neumann postulated two clinical types of thrombosis, based on the site of origin: (1) a benign variety, starting in the veins of the legs and characterized by slow progression of the clots, increasing in frequency with age and having a tendency toward multiple but nonfatal pulmonary embolism; (2) a malignant form, centered in the plantar region and typified by rapidly progressing thrombosis occurring in younger people, not rising in frequency with age and tending toward fulminating, fatal embolism of the lungs. He expressed the belief that the source of emboli for both types is a thrombus that has progressed into the veins of the thigh. In progressive ascending thrombosis, segmentation of the clots results at over-crossings by ligaments, tendons and similar structures, and under these thrombi are usually lacking. Much stress is laid on flat feet, as a cause both of plantar thrombosis and of its localization to the vena plantaris lateralis. Persons with normal or

high arches usually had occlusion of all plantar veins rather than of the vena plantaris lateralis alone.

Two venous over-crossings, designated "proximal plantar venous point" and "distal plantar venous point" are believed by Neumann to be of importance with respect to segmentation of thrombi in the lateral plantar veins, since these points can be projected on the sole of the foot by a special method and are therefore clinically significant for the timely recognition of malignant plantar venous thrombosis. The proximal point is easily found, because it lies under the internal malleolus close to the calcaneus. The distal one is mapped out by measuring the greatest breadth of the sole over the heel and again over the ball of the foot, drawing a line through the midpoint of each and connecting the lines by a third. The highest point of the internal malleolus and the median tubercle of the first metatarsal bone are next connected by a line, and at the midpoint of this another line is drawn perpendicularly across the sole until it bisects the one previously made on the plantar aspect. Where these intersect is the "distal venous point." The accuracy of this observation was checked anatomically by inserting needles and dissecting along their course. The vena plantaris lateralis was never missed by more than 2 mm. Payr [9] and Tschmarke [10] have described pressure pain over the proximal plantar venous point as a delicate sign of incipient thrombosis of the foot, and Neumann has expressed the belief that the sign appears still earlier at his distal point. Olow [11] has said that in venous thrombosis of the calf pain can be elicited at the junction of the gastrocnemius muscle and the achilles tendon, and Krieg [12] asserted that pain on pressure over the distal end of the adductor canal is an indication of thrombosis of the veins of the thigh.

Of Neumann's subjects with thrombosis of the lower extremities, 11.8 per cent had fulminating fatal pulmonary embolism, and more than 80 per cent of these exhibited clots in the veins of the feet and calves. If the cases of nonfatal multiple pulmonary emboli are included, the lower extremities account for 52.8 per cent of the clots lodging in the lungs. Neumann's strong conviction that the so-called "malignant" type of thrombosis, centered in the plantar veins, occurs at an earlier age than

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9. Payr, E.: Gedanken und Beobachtungen über die Thrombo-Emboliefrage. Anregung zu einer Sammelforschung, Zentralbl. f. Chir. **57**:961, 1930; cited by Neumann.[3]

10. Tschmarke, G.: Erfahrungen über den Fuss-sohlendruckschmerz als Frühsymptom der Thrombose, Chirurg **3**:924, 1931; abstracted, München. med. Wchnschr. **78**:2135, 1931; cited by Neumann.[3]

11. Olow, J.: Sur un detail concernant le diagnostic de la thrombose crurale, Acta obst. et gynec. Scandinav. **10**:159, 1930, cited by Neumann.[3]

12. Krieg, E.: Zum klinischen Bild der infektiösen Fernthrombose, München. med. Wchnschr. **82**:776, 1935; cited by Neumann.[3]

involvement of the veins of the calf appears to be based on the fact that the 3 youngest persons of his series, all under 20 years of age, harbored such thrombi. However, reference to the text and to his table 2 shows that plantar thrombosis varies but little among the different age groups.

For reasons mentioned earlier we were seldom able to dissect the veins of the whole lower extremity. In the small number of patients who could thus be studied, occlusion of the plantar veins was observed only once. Fifteen surgically amputated legs were available for critical study; again only 1 instance of thrombosis was found in the sole of the foot. Admittedly our observations are too few to allow for any conclusions, but as far as they go are not in accord with Neumann's findings.

Neumann, in common with many others, has laid great emphasis on the frequent absence of thrombi in the veins of the thigh in cases of pulmonary embolism, even though the veins of the calf are full of antemortem clots. Neumann traced only 18 per cent of fulminating embolism to the veins of the leg. Both he, and Rössle,[2] supported the empiric observation that massive embolic exodus from leg veins rarely results fatally. It is generally admitted that venous thrombi tend to propagate toward the heart, placing the newest part of the clot proximally. We concur with the latter observation. If this is true, is it not both possible and probable that the primary seat of thrombosis is the calf or even the foot and that there would be no thrombosis of the femoral veins if clotting did not first take place peripherally? True, it may be the propagated portions that become massive and fatal emboli, but have physicians not heretofore paid altogether too much attention to the larger and more apparent clots and forgotten the real source of the trouble? The matter is of more than academic interest, for if anything is to be done to prevent the initial clotting it is most important that attention be focused on the primary seat and action not delayed until extension into large veins has had time to take place.

Belt [13] in answer to a query as to whether the "leg veins" listed in his splendid study [14] meant those of the calf, stated that his explorations were largely confined to the femoral and saphenous veins, from which the emboli seemed to come, and added significantly: "I have always felt the thrombosis was not primary in these vessels but began in the smaller vessels of the lower leg."

The most recent thorough investigation is that of Frykholm.[4] The veins of the muscles of the calf were involved in 39 cases; clots occurred in the posterior tibial and peroneal veins 25 times; the veins of the

13. Belt, T. H.: Personal communication to the authors, 1939.

14. Belt, T. H.: Thrombosis and Pulmonary Embolism, Am. J. Path. **10**: 129, 1934.

adductor muscles of the thigh were thrombosed in 16 cases and in 9 others the deep femoral vein was simultaneously blocked; the pelvic veins were implicated only 8 times. The gross observations were amply supplemented by microscopic studies. Frykholm also dissected the veins of the gluteal region, the extensor musculature of the lower extremities and the anterior tibial veins. The results were negative. Only 2 dissections of the plantar veins are recorded; 1 revealed a thrombus in the posterior tibial vein posterior to the malleolus. There were 24 instances of pulmonary embolism, but the author failed to state which of the possible sources appeared to be responsible. Always progression of the thrombotic process was in the direction of the blood stream; retrograde extension was a rarity. It is Frykholm's concept that during confinement to bed the thin walls of the veins collapse from mechanical pressure, allowing intima to contact intima, especially in the adductor muscles and the muscles of the calf, which take the least part in active movement while a person is in bed and through which minimal amounts of blood pass. Since normal metabolism of the intima depends on its contact with the circulating blood, collapse may easily disturb the nutrition of the endothelium and in this way become an important primary condition leading to thrombosis by giving off substances from the damaged endothelium which promote coagulation of blood. He conceived that it is also possible for the plantar and the pelvic veins to collapse under certain circumstances, with like results.

PROPHYLAXIS AND TREATMENT

From our own study and from the writings of others, it would appear that there is no one cause for thrombosis of the veins of the leg. Although it would be short sighted not to admit that a number of factors may operate, we are strongly of the opinion that the major role is played by forced recumbency of adult persons who prior to an illness or operation have been active or at least ambulatory. Then, all too frequently, these people are put to bed for varying periods of time and allowed to lie quietly, without recognition of the simple physiologic principle that gravity and muscular activity are of major importance in the efficient return of venous blood from the extremities. Or, worse still, pillows are supplied for the comfort of the patient and the already anatomically existent "bottle neck" at the popliteal vein is enhanced, or the hospital bed is broken at the middle and the same bad situation is produced.

Many authors have stressed the value of exercise in bed and the importance of early rising with respect to thrombus prevention, so we make no claim to originality in asserting our firm belief that a fundamental therapeutic procedure, unless there are definite contraindications,

is the prescription of periodic, active flexion and extension of the feet, legs and thighs, frequent turning of helpless patients, prevention or relief of abdominal distention, and deep breathing exercises throughout the period of rest in bed. Orders for these measures should be written on the hospital chart by the physician, who should then see to it that the nurses are carrying out his instructions. It is well to have the patient demonstrate to the physician so that any alterations or corrections can be made. This serves well as a check on the nurse in charge. Since the sensation of scraping of the toes against the sheet is unpleasant, better cooperation will be obtained by loosening the bedding or by having the patient lie on his side while exercising. Some patients prefer to have something solid to push against and will do better by being allowed to slide down until the feet contact the end of the bed. The variable resistance bicycle pedal device recently described by de Takáts and Jesser [15] would appear ideal for such a purpose. Homans [16] recommended elevation of the foot of the bed, which will enable gravity to aid the return of venous blood. Frykholm [4] raised the head of the bed, necessitating movement of the patient to overcome the sensation of sliding downward.

Active motion is vastly superior to passive movement or massage. The latter is definitely contraindicated unless it is started immediately after confinement. Our observation of several instances of thrombus formation within three days after a patient's going to bed leads us to believe that even active movement cannot be employed with impunity unless it is instituted soon after the beginning of recumbency. If exercise is delayed for even a few days, there is at least potential danger of dislodging portions of fresh thrombi. A patient already ill for a few days before a physician is consulted had best be allowed to remain quiet.

While determination of the prothrombin content of the blood will aid in detecting persons who are likely to have thrombosis, it is not readily done routinely. The use of heparin to inhibit clotting has likewise been suggested for the prevention of thrombosis, but the cost will make its use limited. On the other hand, exercise costs nothing beyond a little additional work for the nursing staff, and the principle of using it is sound, not only physiologically but psychologically, since the patient's mind is kept occupied and muscle tone is maintained.

While the emphasis should be on prevention, some means of treatment must be at hand for patients in whom small emboli have demon-

15. de Takáts, G., and Jesser, J. H.: Pulmonary Embolism, J. A. M. A. **114**: 1415 (April 13) 1940.

16. Homans, J.: Varieties of Thrombophlebitis of the Limbs: Their Origin, Course and Treatment, Am. J. Surg. **44**:3, 1939.

strated their presence. Homans [16] advised ligation of the femoral vein under such circumstances.

SUMMARY

Thrombosis of the deep veins of the leg is appallingly frequent among middle-aged and older persons forced to bed for varying periods of time. The incidence in the present study was 52.7 per cent.

Bilateral involvement was found 110 times and unilateral 75 times. The right side alone was affected a little more often than was the left. Thrombi formed in the veins accompanying the larger arteries far more frequently than in other veins and were present in the soleus muscle more often than in the gastrocnemius.

Fatal pulmonary embolism was responsible for 3.13 per cent of all deaths; in 45.4 per cent of the cases of death from such embolism the most probable source was thrombosed leg veins. There is good authority for the belief that although fulminating emboli often spring from the femoral vessels, thrombosis here represents an extension from older clots in the legs and feet. From the standpoint of prophylaxis and treatment, recognition of this is most important.

Lesser emboli frequently originate from the veins of the calf. Showers of these, even though of small diameter, may consist of long clots, which, by buckling or coiling, are capable of occluding even the major pulmonary arteries. Repeated embolic episodes are more frequent than a single massive attack. Multiple small fragments can also do harm, by placing an added burden on an already embarrassed circulatory system.

In the present series there was little difference in the incidence of thrombosis between medical and surgical patients or between males and females.

Phlebitis, either as a cause or as a complication of thrombosis, had a minor role in our cases.

As a rule, phlebothrombosis of the deep veins of the leg is clinically silent and for this reason is likely to be forgotten until embolic phenomena appear.

We are of the opinion that the greatest single factor favoring thrombus formation in the lower extremity is sudden confinement to bed of a previously ambulatory older person without the benefit of active exercise or the aid of gravity in the maintenance of an efficient venous circulation.

Planned and supervised voluntary movement and the elimination of too much comfort for the legs should do much to reduce incidence of thrombosis and its all too frequent sequel—pulmonary embolism.

SERUM LIPIDS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND IN PATIENTS WITH OBSTRUCTIVE JAUNDICE

A COMPARATIVE STUDY

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In 1933 Hench [1] reported the analgesic effect of jaundice in cases of chronic arthritis, fibrositis and sciatic pain and followed this report with several papers on further observations of the phenomenon. Sidel and Abrams,[2] Borman,[3] and others have confirmed these observations. Hench stated that bilirubin appears to be the most likely agent responsible for the beneficial effect of jaundice on arthritis. This appears true in view of Race's findings [4] that the icteric index and the concentration of serum bilirubin are likely to be low among patients who have rheumatoid arthritis. However, Hench suggested the possibility that bile salts, hepatic autolysate, special diet or other factors may be responsible

From the Rackham Arthritis Research Unit, the Medical School, University of Michigan. The Rackham Arthritis Research Unit is supported by the Horace H. Rackham School of Graduate Studies.

1. Hench, P. S.: Analgesia Accompanying Hepatitis and Jaundice in Cases of Chronic Arthritis, Fibrositis and Sciatic Pain, Proc. Staff Meet., Mayo Clin. **8**:430-436 (July 12) 1933; Analgesia Accompanying Hepatitis and Jaundice in Cases of Chronic Arthritis, J. A. M. A. **101**:1265-1266 (Oct. 14) 1933; The Analgesic Effect of Hepatitis and Jaundice in Chronic Arthritis, Fibrositis and Sciatic Pain, Ann. Int. Med. **7**:1278-1294 (April) 1934; A Clinic on Some Diseases of Joints: IV. The Inactivation of Chronic Infectious Arthritis and Fibrositis by Jaundice, M. Clin. North America **19**:573-583 (Sept.) 1935; Effect of Jaundice on Chronic Infectious (Atrophic) Arthritis and on Primary Fibrositis: Further Observations; Attempts to Reproduce the Phenomenon, Arch. Int. Med. **61**:451-480 (March) 1938.

2. Sidel, N., and Abrams, M. I.: Jaundice in Arthritis: Its Analgesic Action, New England J. Med. **210**:181-182 (Jan. 25) 1934.

3. Borman, M. C.: Jaundice in Arthritis, with Report of Two Cases, Wisconsin M. J. **35**:890-891 (Nov.) 1936.

4. Race, J.: Biochemical Investigation in Chronic Rheumatic Diseases: Report on Chronic Rheumatic Diseases, London, H. K. Lewis & Co., Ltd., 1935, no. 1, pp. 55-71.

for the phenomenon. Assuming that the responsible agent ("factor X") is a specific chemical substance or a combination of substances and not a nonspecific set of circumstances, Hench further speculated that this phenomenon results from (*a*) the correction of some chemical deficiency, (*b*) the correction of some chemical oversufficiency or (*c*) a process of bacteriolysis, bacteriostasis or detoxification.

Hench attempted to produce therapeutic jaundice by administering bilirubin, bile salts, synthetic bile salts, diluted ox bile, human bile and liver extracts and by transfusions of blood from highly jaundiced persons, with disappointing results. Wolff,[5] McGowan[6a] and McGowan, Bollman and Mann[6b] suggested the use of toluylenediamine to produce artificial jaundice, but Hench[1] found this type of jaundice to be ineffective against arthritic pain. Thompson and Wyatt[7] observed that the bilirubin level in the serum of patients with arthritis averaged 1.39 mg. per hundred cubic centimeters, as compared with the average of 2.06 mg. in normal persons. They were able to induce nontoxic jaundice by the injection of bilirubin dissolved in sodium carbonate plus a solution of the sodium salt of dehydrocholic acid, and this jaundice had an ameliorating effect on the symptoms of rheumatoid arthritis; the administration of either bile salts or bilirubin alone did not produce jaundice, nor was there any clinical benefit therefrom.

Most attempts to isolate this "factor X" in jaundice which produces relief from arthritis have been made with the idea that bilirubin, bile salts or bile acids are responsible. In our study attention has been turned to other abnormal constituents of the blood in persons with jaundice, the lipids. A comparative study of the lipid partition of serum was made on patients with obstructive jaundice, on patients with rheumatoid arthritis and on normal subjects for the following reasons: (1) to establish the existence or absence of any abnormality in the serum lipid values of persons with arthritis; (2) to compare the serum lipids in patients with arthritis with those present in persons with obstructive jaundice, and (3) to determine whether changes in serum lipids associated with obstructive jaundice could be the basis for the beneficial effect of jaundice on rheumatoid arthritis.

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5. Wolff, H. J.: The Physiologic Action of Toluylendiamin and Its Relation to Experimental Jaundice, J. Pharmacol. & Exper. Therap. **50**:407-419 (April) 1934.

6. (*a*) McGowan, J. M.: Bile Salts in Toluylenediamine Jaundice, Proc. Staff Meet., Mayo Clin. **10**:565-567 (Sept. 4) 1935. (*b*) McGowan, J. M.; Bollman, J. L., and Mann, F. C.: The Bile Acids in Icterus Produced by Toluylenediamine, J. Pharmacol. & Exper. Therap. **58**:305-311 (Nov.) 1936.

7. Thompson, H. E., and Wyatt, B. L.: Experimentally Induced Jaundice (Hyperbilirubinemia): Report of Animal Experimentation and of the Physiologic Effect of Jaundice in Patients with Atrophic Arthritis, Arch. Int. Med. **61**:481-500 (March) 1938.

PROCEDURE

Subjects.— Studies were made on 12 patients with arthritis. Eleven of these had typical rheumatoid arthritis; 7 were men and 4 were women. Their ages varied from 29 to 56; the duration of disease ranged from four months to twenty years. One patient (L. D.) with spondylitis rhizomelica was studied; he was 28 years of age, and the disease had existed for six years at the time of this study.

Serum Values in Normal Subjects, in Patients with Arthritis and in Patients with Obstructive Jaundice

Subject	Age	Sex	Duration of Disease, Mo.	Days on Diet	Total Lipid, Mg. per 100 Cc.	Phospholipid, Mg. per 100 Cc.	Iodine	Cholesterol: Total, Mg. per 100 Cc.	Cholesterol: Free, Mg. per 100 Cc.	Cholesterol: Ester, Mg. per 100 Cc.	Cholesterol: Ester Percentage	Bilirubin, Mg. per 100 Cc.
Patient with rheumatoid arthritis												
R. J.	51	M	240	0	624	208	67	183	45	138	75.4	...
M. R.	56	F	72	0	794	227	63	140	44	96	68.6	...
M. K.	30	M	18	0	926	267	66	243	53	190	78.2	...
L. D.	28	M	72	0	471	242	74	127	36	91	71.7	...
C. M.	46	F	90	0	390	222	70	112	31	72	64.3	...
D. L.	45	F	36	7	506	170	80	189	44	145	76.7	...
P. S.	53	M	24	7	610	218	61	156	43	113	72.4	...
H. G.	42	M	60	7	447	...	77	165	38	127	77.0	...
R. S.	35	M	24	7	545	311	68	134	33	101	75.4	...
G. C.	55	F	36	0	515	295	73	214	58	156	72.9	...
K. N.	29	M	96	7	498	217	61	139	39	100	71.9	...
S. G.	52	M	4	7	583	425	65	124	33	91	73.4	...
Average	..	..	..	..	584	255	69	161	41	118	73.2	
Patients with jaundice												
R. S.	55	M	..	0	1,108	586	56	130	80	50	38.5	9.0
E. L.	38	F	..	0	2,026	1,093	59	330	151	179	54.2	5.0
S. S.	70	F	..	0	598	347	70	204	52	152	74.5	5.8
G. S.	52	M	..	0	1,580	941	46	313	264	49	15.7	16.0
H. K.	50	M	..	0	2,166	1,016	50	422	290	132	31.3	4.6
Average	..	..	..	..	1,496	797	56	280	167	112	42.8	8.1
Normal controls												
R. A.	23	F	..	7	559	177	66	97	29	68	70.1	
M. D.	22	F	..	7	510	157	60	162	38	124	76.5	
A. C.	38	F	..	7	553	...	85	195	58	137	70.3	
R. F.	35	M	..	0	610	226	73	210	47	153	72.9	
Average	..	..	..	..	558	187	71	163	43	121	72.5	

Five patients with obstructive jaundice were studied; 3 were men and 2 were women; their ages varied from 38 to 70. Three of these patients (R. S., E. L. and S. S.) suffered from biliary obstruction due to carcinoma of the head of the pancreas. One patient (G. S.) had cirrhosis of the liver, and another (H. K.) had obstructive jaundice due to gallstones in the common bile duct.

Four normal subjects were studied as controls; 3 were women whose ages varied from 22 to 28, and 1 was a 35 year old man.

Preparation of Subjects.—All samples of blood were taken from subjects after a twelve hour fasting period. Whenever possible, identical diets of approximately 2,400 calories per day were fed for seven days preceding the venipuncture. This

diet consisted of 80 Gm. of protein, 175 Gm. of carbohydrate and 150 Gm. of fat. Six of the 12 patients with arthritis and 3 of the 4 controls were fed this diet (table 1). Because of gastrointestinal difficulties it was impossible for the jaundiced patients to eat this diet.

Chemical Methods.—Fifty to 60 cc. of blood was taken, allowed to clot and centrifuged. Twenty-five cubic centimeters of serum was then extracted by the ether-alcohol procedure of Bloor,[8] evaporated to dryness in vacuo, dissolved in purified petroleum benzine U. S. P. (petroleum ether) and made up to a volume of 100 cc. Aliquots of this stock solution were used in the determinations. Gravimetric determinations of total lipids were carried out in duplicate. Phospholipid determinations were made in triplicate by an adaptation to the Evelyn photoelectric colorimeter of the Fiske-Subbarow aminonaphthol-sulfonic acid-phosphate method [9] after precipitation of the phospholipids with acetone according to the method of Bloor.[10] Total and free cholesterol were determined in triplicate analyses by an adaptation to the photoelectric colorimeter of the Schoenheimer-Sperry method [11] of precipitation with digitonon, and ester cholesterol values were calculated by difference. The iodine value was determined by the pyridine sulfate dibromide method of Rosenmund and Kuhnhenn,[12] and the bilirubin concentration was measured by the van den Bergh method.[13]

RESULTS

Results of all the analyses appear in the table. The total lipid values for the group of patients with arthritis varied from 399 to 926 mg. per hundred cubic centimeters, with an average of 584 mg., as compared with 558 mg. for the control group. The iodine values averaged 69 for the former and 71 for the latter. Analyses for serum phospholipids in the former group gave an average of 255 mg. per hundred cubic centimeters, in contrast to an average of 187 mg. in the latter group. Average values of 161, 41 and 118 mg. per hundred cubic centimeters were found for total, free and ester cholesterol, respectively, in the group of patients with arthritis, while the control group had average values of 166, 43 and 121 mg. The percentage of cholesterol present in the ester form was essentially the same in the two groups, as shown by the averages of 73.2 for the patients with arthritis and 72.5 for the controls.

In the group of patients with jaundice the total serum lipids varied from 598 to 2,166 mg. per hundred cubic centimeters, with an average

8. Bloor, W. R.: The Determination of Small Amounts of Lipid in Blood Plasma, J. Biol. Chem. **77**:55-73 (April) 1928.

9. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375-400 (Dec.) 1925.

10. Bloor, W. R.: The Oxidative Determination of Phospholipid (Lecithin and Cephalin) in Blood and Tissues, J. Biol. Chem. **82**:273-286 (May) 1929.

11. Schoenheimer, R., and Sperry, W. M.: A Micro Method for the Determination of Free and Combined Cholesterol, J. Biol. Chem. **106**:745-760 (Sept.) 1934.

12. Rosenmund, K. W., and Kuhnhenn, W.: Eine neue Methode zur Jodzahlbestimmung in Fetten und Ölen unter Verwendung von Pyridinsulfardibromid, Ztschr. f. Untersuch. d. Nahrungs- u. Genussmittel **46**:154-159, 1923.

13. van den Bergh, A. A. H.: Der Gallenfarbstoff in Blute, Leiden, 1918.

value of 1,496. The iodine value averaged 56.2, and the levels of serum phospholipid averaged 797 mg. per hundred cubic centimeters. The average values for total, free and ester cholesterol were 280, 167 and 112 mg. per hundred cubic centimeters, respectively. The average percentage of esterified cholesterol was 42.8.

COMMENT

Previous studies on the lipid fractions of the blood in rheumatoid arthritis have led to contradictory results. Kauftheil [14] found high cholesterol values during severe inflammation in cases of rheumatoid arthritis and normal values when the inflammation subsided. Bruger [15] and his co-workers reported a decrease in total cholesterol with a normal relationship between the free and ester fractions, while Gorham and Meyers [16] and Pemberton and Foster [17] found normal values for total cholesterol in patients with arthritis. Our results show similar values for total, free and ester cholesterol in the group of patients with arthritis and in the control group, and likewise the percentage of esterified cholesterol is nearly identical in the two groups, which confirms the results of the latter workers.

In 4 of the 5 patients with jaundice, the total values for serum lipids were extremely high, and in all patients the serum phospholipids were increased to values two to three times those of the normal subjects. White, Deutsch and Maddock [18] found similar increases in phospholipids

14. Kauftheil, L.: Ueber den Cholesteringehalt des Blutserums bei Gelenkerkrankungen, Wien. Arch. f. inn. Med. **19**:273-284 (Nov.) 1929.

15. (*a*) Bruger, M., and Poindexter, C. A.: Relation of the Plasma Cholesterol to Obesity and to Some of the Complicating Degenerative Diseases (Diabetes Mellitus, Essential Hypertension, Osteoarthritis and Arteriosclerosis), Arch. Int. Med. **53**:422-434 (March) 1934. (*b*) Hartung, E. F.; Greene, C. H., and Bruger, M.: Calcium and Cholesterol Metabolism in Arthritis, Proc. Am. A. Study & Control Rheumat. Dis., 1934, p. 14. (*c*) Hartung, E. F., and Bruger, M.: The Cholesterol Content of the Plasma in Arthritis, J. Lab. & Clin. Med. **20**:675-681 (April) 1935.

16. Gorham, F. D., and Myers, V. C.: Remarks on the Cholesterol Content of Human Blood, Arch. Int. Med. **20**:599-612 (Oct.) 1917.

17. (*a*) Pemberton, R.: Arthritis and Rheumatoid Conditions, ed. 2, Philadelphia, Lea & Febiger, 1935. (*b*) Pemberton, R., and Foster, G. L.: Studies on Arthritis in the Army Based on Four Hundred Cases: III. Studies on the Nitrogen, Urea, Carbon Dioxide Combining Power, Calcium, Total Fat and Cholesterol of the Fasting Blood, Renal Function, Blood Sugar and Sugar Tolerance, Arch. Int. Med. **25**:243-282 (March) 1920.

18. White, F. W.; Deutsch, E., and Maddock, S.: (*a*) The Comparative Value of Serial Hippuric Acid Excretion, Total Cholesterol, Cholesterol Ester, and Phospholipid Tests in Diseases of the Liver: I. The Results of the Tests, Am. J. Digest. Dis. **6**:603-610 (Nov.) 1939; (*b*) II. A Clinical Comparison of the Tests, ibid. **6**:3-7 (Jan.) 1940.

in 90 per cent of their patients with obstructive jaundice, and Chanutin and Ludewig [19] observed an increase in the plasma phosphatide phosphorus in rats with ligated bile ducts.

The total cholesterol values were above normal in 4 of our 5 patients with jaundice, and free cholesterol was high in all, the average value being four times the normal level. The hypercholesteremia observed in these patients with obstructive jaundice is in agreement with the results obtained in man by Epstein,[20] Wilkinson [21] and White, Deutsch and Maddock,[18] in dogs by Hawkins and Wright [22] and in rats by Chanutin and Ludewig.[19] The latter workers also found a direct proportionality between the free cholesterol and the phospholipid phosphorus, while our results only roughly show such a proportionality.

Our findings indicate that the ester cholesterol was below normal in 2 cases and above normal in 3 while in 4 cases the failure of the ester cholesterol to parallel the increase in the free cholesterol resulted in a lowered cholesterol-ester ratio. Epstein [20] reported similarly varying ratios; in half of his cases of obstructive jaundice the esters rose proportionately with the free cholesterol; in other cases the ester fraction did not rise sufficiently to maintain the normal ratios, and in 8 of 43 cases there was a fall in cholesterol esters. White, Deutsch and Maddock [18] found that in 80 per cent of their patients the cholesterol ester values were below their normal value of 60 per cent of the total cholesterol. Chanutin and Ludewig [19] reported that the plasma cholesterol esters in rats with ligated bile ducts were normal or slightly above normal, but that the rise in free cholesterol resulted in a lowered ratio of ester cholesterol to total cholesterol.

No correlation could be found between the bilirubin levels and the total serum lipids or any lipid fraction. One patient with jaundice (S. S.) had normal values for total serum lipids and cholesterol, but the level of serum phospholipid was high.

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19. Chanutin, A., and Ludewig, S.: The Blood Plasma Cholesterol and Phospholipid Phosphorus in Rats Following Partial Hepatectomy and Following Ligation of the Bile Duct, J. Biol. Chem. **115**:1-7 (Aug.) 1936.

20. (*a*) Epstein, E. Z.: The Cholesterol Partition of the Blood Plasma in Parenchymatous Diseases of the Liver, Arch. Int. Med. **47**:82-93 (Jan.) 1931; (*b*) Cholesterol of the Blood Plasma in Hepatic and Biliary Disease, ibid. **50**: 203-222 (Aug.) 1932. (*c*) Epstein, E. Z., and Greenspan, E. B.: Clinical Significance of Cholesterol Partition of the Blood Plasma in Hepatic and Biliary Disease, ibid. **58**:860-890 (Nov.) 1936.

21. Wilkinson, S. A.: Cholesterol Metabolism in Jaundice, Am. J. Digest. Dis. & Nutrition **3**:618-622 (Nov.) 1936.

22. Hawkins, W. B., and Wright, A.: Blood Plasma Cholesterol Fluctuations Due to Liver Injury and Bile Duct Obstruction, J. Exper. Med. **59**:427-439 (April) 1934.

There were no definite abnormalities in the total serum lipids or in any of its fractions in patients with arthritis. The therapeutic results secured by jaundice might lead to the premise that these results are due to elevation of serum lipids such as that obtained during obstructive jaundice. However, if this assumption is correct one might expect a low level of serum lipids in persons with arthritis, in contrast to the high level of serum lipids in patients with jaundice, so that the jaundice might act as though correcting a deficiency state. However, no such opposite values for serum lipids were found, and such a mechanism for the beneficial results of jaundice cannot be concluded. However, the extremely high values for phospholipids and for total and free cholesterol observed in persons with jaundice may be a factor in the phenomenon of the analgesic effect of jaundice.

SUMMARY

In patients with arthritis the ratio of ester cholesterol to total cholesterol was normal. The values for total, free and ester serum cholesterol were found to be nearly identical with the values in normal control subjects. Normal values for total serum lipids were obtained from persons with arthritis, whereas levels of serum phospholipids were slightly elevated.

In patients with obstructive jaundice, the levels of total serum lipids and serum phospholipids were extremely high, the levels of total and free cholesterol were markedly increased over normal levels and the percentage of cholesterol combined in the ester form was far below that found in normal subjects.

The serum lipids in patients with arthritis are not below normal; hence jaundice is not beneficial to arthritic patients by reason of correcting a lipid deficiency, but it is possible that the extremely high levels of total lipids, phospholipids and total and free cholesterol which are present in jaundice may be a factor in causing the beneficial effect of jaundice on arthritis.

IMMEDIATE SERUM REACTIONS IN MAN

CLASSIFICATION AND ANALYSIS OF REACTIONS TO INTRAVENOUS ADMINISTRATION OF ANTIPNEUMOCOCCUS HORSE SERUM IN CASES OF PNEUMONIA

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Since Jan. 1, 1937 reports on the use of concentrated antipneumococcus serum have been submitted on a uniform record to the New York State Department of Health by physicians employing serums produced or purchased and distributed by the Division of Laboratories and Research.[1] The questions on that form are concerned, so far as possible, with objective data, so that the effect of interpretation by the reporting physician is minimized. Through a follow-up system, complete reports were obtained in practically every case.[2]

Early study of the material so collected brought to light a number of immediate reactions following intravenous serum therapy which were associated with severe circulatory collapse and which did not seem to be related to protein hypersensitivity in the usual sense. It was recognized that this impression was based on reports which had the disadvantage of containing second hand information of varying degrees of accuracy. In order to obtain further information regarding such reactions, the literature was reviewed and a study undertaken.

A review of the literature on serum reaction disclosed many reports of the occurrence of death during the administration of serum, which

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From the Bureau of Pneumonia Control, New York State Department of Health.

This study received financial aid in part from the Metropolitan Life Insurance Company and in part from the Commonwealth Fund.

1. Physicians and hospitals throughout the state of New York cooperated in this study.

2. Rogers, E. S.; Rutstein, D. D., and others: Study of Antipneumococcus Horse Serum in the Treatment of More than Five Thousand Cases, to be published.

are well summarized for all types of serum therapy up to 1930 [3] and for the serum treatment of pneumonia up to 1939.[4] Additional reports have been made since that time.[5] Studies have been published presenting the relationship to reactions of previous injections of serum,[6] positive cutaneous reactions,[7] the amount of serum injected [8] and the concentration of the serum.[9] Most of these studies failed to differentiate between immediate serum reactions and the delayed reaction, or "serum sickness." [10] There were also expositions regarding the nature of serum

3. (*a*) Lamson, R. W.: Sudden Death Associated with Injection of Foreign Substances, J. A. M. A. **82**:1091-1098 (April 5) 1924. (*b*) Bullowa, J. G. M., and Jacobi, M.: Fatal Human Anaphylactic Shock: Report of a Case, with Autopsy Observations and Review of the Literature, Arch. Int. Med. **46**:306 (Aug.) 1930.

4. Heffron, R.: Pneumonia with Special Reference to Pneumococcus Lobar Pneumonia, New York, The Commonwealth Fund, 1939, p. 863.

5. (*a*) Waldbott, G. L.: Prevention of Anaphylactic Shock with Study of Nine Fatal Cases, J. A. M. A. **98**:446-449 (Feb. 6) 1932; (*b*) Allergic Death: Protracted Shock, Arch. Int. Med. **54**:597-605 (Oct.) 1934. (*c*) Tuft, L.: Fatalities Following Reinjection of Foreign Serum: Report of Unusual Case, Am. J. M. Sc. **175**:325-331 (March) 1928. (*d*) Freedman, H. J.: Acute Anaphylactic Shock Following Intracutaneous Test for Sensitivity to Horse Serum: Report of Fatal Case, New England J. Med. **212**:10 (Jan. 3) 1935.

6. (*a*) Lyall, H. W., and Murdick, P. P.: Tetanus Antitoxin: Serum Reactions Following Prophylactic Injection, New York State J. Med. **38**:882-885 (June 1) 1938. (*b*) Hooker, S. B.: Human Hypersensitiveness Induced by Very Small Amounts of Horse Serum, J. Immunol. **9**:7-16 (Jan.) 1924. (*c*) Park, W. H.: Human Hypersensitiveness to Whole Serum or Serum Globulins Following Diphtheria Toxin Antitoxin Injections: Its Importance, ibid. **9**:17-24 (Jan.) 1924. (*d*) Bauer, E. L., and Wilmer, H. B.: Toxin Antitoxin: Hypersensitivity to Its Protein Content, J. A. M. A. **86**:942 (March 27) 1926. (*e*) Spicer, S.: Effect of Previous Administration of Antitoxin and Toxin Antitoxin on Serum Reaction, ibid. **90**:1778-1779 (June 2) 1928.

7. Davis, H. M.: Horse Serum Skin Tests, J. Hyg. **38**:325-330 (May) 1938. Clairborn, L. N.: Ophthalmic Test for Sensitivity to Horse Serum, J. A. M. A. **98**:1718-1720 (May 14) 1932. Spicer, S.: Ophthalmic Test for Horse Serum Sensitivity Contrasted with Intradermal, Performed on Three Hundred and Fifty-Three Patients, J. Immunol. **15**:335-342 (July) 1928. Lyall and Murdick.[6a]

8. (*a*) Gerlough, T. D.: Relation of Incidence of Serum Disease to Square Root of Amount of Antiserum Injected, J. Infect. Dis. **56**:317-320 (May-June) 1935. (*b*) Hunt, L. W.: Recent Observations in Serum Disease, J. A. M. A. **99**:909-912 (Sept. 10) 1932.

9. Park, W. H., and Throne, B.: The Results of the Use of Refined Diphtheria Antitoxin, Gibson's "Globulin Preparation," in the Treatment of Diphtheria, Am. J. M. Sc. **132**:686 (Dec.) 1906. Rosenau, M. J., and Anderson, J. F.: Studies upon Hypersusceptibility and Immunity, Hygienic Laboratory Bulletin 36, United States Treasury Department, Public Health Service, 1907. Weaver, G. N.: Serum Disease, Arch. Int. Med. **3**:485 (Aug.) 1909. Lyall and Murdick.[6a] Hunt.[8b]

10. von Pirquet, C. F., and Schick, B.: Die Serumkrankheit, Leipzig, Franz Deuticke, 1905.

reactions in man,[11] the interpretation of the mechanism of which usually was based on the results of animal experimentation.

The enormous literature on reactions in animals will not be reviewed here, as excellent summaries are available.[12] One of the outstanding facts evident in that literature is the wide variation in the response to the injection of foreign proteins, depending on the species of animal used.[13] Such differences emphasize the need for greater caution in attempting to interpret the symptoms occurring during serum reactions in man on the basis of experiments performed on other animal species.

No report was found of serum treatment of human subjects in which a tabulation, a classification and an analysis of all immediate reactions were presented. This lack of data probably is inherent in the fact that the relative infrequency of such reactions in the experience of any one physician or hospital precludes the possibility of a comprehensive study.

In order to increase the accuracy of the reports which indicated the occurrence of immediate serum reactions, a personal visit was made to the majority of physicians reporting such reactions during the period from Jan. 1 to Oct. 1, 1938. Also included in this investigation were reports indicating a history of allergy, a positive cutaneous or ophthalmic test with horse serum or death within eight hours of the administration

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11. (*a*) Mackenzie, G. M., and Hanger, F. M.: Serum Disease and Serum Accidents, J. A. M. A. **94**:260-265 (Jan. 25) 1930. (*b*) Rackemann, F. M.: Clinical Allergy, New York, The Macmillan Company, 1931. (*c*) Rudolph, J. A., and Cohen, M. B.: Types of Human Hypersensitiveness: Their Relationship to Liability to Serum Reactions, J. A. M. A. **102**:900 (March 24) 1934. (*d*) Seegal, B. C., in Gay, F. P., and others: Agents of Disease and Host Resistance, Springfield, Ill., Charles C. Thomas, Publisher, 1935, chap. 6, p. 36.

12. Wells, H. G.: Present Status of Problems of Anaphylaxis, Physiol. Rev. **1**:44 (Jan.) 1921. Karsner, H. T., in Jordan, E. O., and Falk, I. S.: Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, chap. 73, p. 966. Topley, W. W. C., and Wilson, G. S.: The Principles of Bacteriology and Immunology, Baltimore, William Wood & Company, 1936, p. 889. Zinsser, H.; Enders, J. F., and Fothergill, L. D.: Immunity: Principles and Application in Medicine and Public Health, New York, The Macmillan Company, 1939, p. 349. Seegal.[11d]

13. Auer, J., and Lewis, P. A.: Acute Anaphylactic Death in Guinea-Pigs: Its Cause and Possible Prevention; a Preliminary Note, J. A. M. A. **53**:458 (Aug. 7) 1909; Physiology of the Immediate Reaction of Anaphylaxis in the Guinea-Pig, J. Exper. Med. **12**:151 (April) 1910. Weil, R.: Liver in Shock and Peptone Poisoning, J. Immunol. **2**:525 (Oct.) 1917. Coca, A. F.: Mechanism of Anaphylaxis Reaction in Rabbit, ibid. **4**:219 (Oct.) 1919. Edmunds, C. W.: Anaphylaxis in the Cat and Opossum, J. Pharmacol. & Exper. Therap. **5**:518 (May) 1914. Parker, J. T., and Parker, F., Jr.: Anaphylaxis in White Rat, J. M. Research **44**:263 (March) 1924. Ritz, H.: Ueber Antikörperbildung und Anaphylaxie bei weissen Mausen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **9**:321 (Aug.) 1911. Kopeloff, N.; Davidoff, L. M., and Kopeloff, L. M.: General and Cerebral Anaphylaxis in Monkey, J. Immunol. **30**:477 (June) 1936.

of serum, even if no reaction occurred. During the interview with the reporting physician, confirmatory and supplementary information was requested and was recorded on a special study form. The hospital record was examined in every case in which hospitalization had occurred, and any other medically trained observers of the reaction, such as interns and nurses, were interviewed. This study also included reactions which were personally observed in patients in the pneumonia service of the Albany Hospital.

For the purpose of the study, an immediate reaction was defined as any untoward change in the patient's condition which was reported as occurring during injection of serum or within two hours of the time injection was started. Serum sickness after that interval was excluded, as it rarely endangers the life of the patient.[14] All gradations of immediate reaction were included, from one spot of urticaria, slight dyspnea or chilly sensations to fatal reactions. No selection of cases for investigation was made.

During the period from Jan. 1 to Oct. 1, 1938, 535 cases out of about 800 reported during that period were investigated according to the aforementioned plan. Of these 535 cases, reactions were found to have occurred in 449. Although this group of investigated cases is included in the larger group of 790 cases in which immediate reactions were reported and which are analyzed in this paper, separate analyses of these two groups led to the same conclusions.

CLASSIFICATION OF REACTIONS

A study of the characteristics of the reactions encountered suggested a logical division into four classes: thermal, anaphylactic, circulatory and miscellaneous. Definitions of these reactions and reports of cases illustrating their clinical picture follow.

Thermal Reaction.—This class included every reaction characterized by chilly sensations or a shaking chill with or without a subsequent rise in temperature and every one with a sudden rise in temperature without a recognizable chill (infrequent) occurring during or shortly after the administration of serum.

Typical case histories exemplifying mild and severe thermal reactions follow:

M. L., an 11 year old white girl, had the onset of pneumonia Feb. 11, 1938. She was hospitalized on February 12. Pneumococcus type I was found in the sputum. The personal history was not remarkable, and there was no history of

14. Clark, E., and Kaplan, B. I.: Endocardial Arterial and Other Mesenchymal Alterations Associated with Serum Disease in Man, Arch. Path. **24**:458-475 (Oct.) 1937. Clark, E.: Serum Carditis: Morphologic Cardiac Alterations in Man Associated with Serum Disease, J. A. M. A. **110**:1098-1100 (April 2) 1938.

allergy. The patient had never received horse serum previously. The cutaneous reaction to 0.1 cc. (1:100 dilution) of horse serum was negative. The ophthalmic reaction to 0.1 cc. (1:10 dilution) horse serum was negative. Administration of serum was begun on February 12, at 2 a. m., when the patient was given 20 cc. of type I antipneumococcus horse serum (lot 42B) diluted with 50 cc. of physiologic solution of sodium chloride over a period of one-half hour; there was no reaction. At 10 a. m. on that day a similar injection of the same amount of type I antipneumococcus horse serum of the same lot number, diluted in the same amount of physiologic solution of sodium chloride, was administered over a period of one-half hour. At the end of the injection the patient coughed and had a moderate shaking chill. The pulse was rapid and was of fair quality. There was no asthma or urticaria. The temperature, which had been 103.2 F., rose to 105.8 F. by 10:45 a. m. The pulse and the respiratory rates remained relatively unchanged. The reaction was followed by an immediate crisis. On February 16 the patient had a severe bout of serum sickness consisting of arthritis, urticaria and lymphadenitis, which persisted for four days. Recovery was then uneventful.

H. Q., a 64 year old man, had the onset of pneumonia March 1, 1938. He was hospitalized on March 7, on which date Pneumococcus type VIII was found in the sputum. The personal history was not remarkable, and there was no history of allergy. It was not known whether serum had been administered previously. The cutaneous reaction to 0.1 cc. (1:100 dilution) of horse serum was negative. Administration of serum was begun at 4:45 p. m. on March 7, when 40 cc. of type VIII antipneumococcus serum (lot 8-05A) in 250 cc. of physiologic solution of sodium chloride was injected intravenously over a period of fifteen minutes. One hour and five minutes later the patient had a severe chill followed by an elevation of temperature from 103.2 to 108 F., of pulse rate from 88 to 146 and of respiratory rate from 24 to 40. He became delirious. The pulse volume remained good throughout the reaction. There was no vascular collapse, asthma or urticaria. The patient received treatment for the symptoms and gradually recovered.

At 10:30 p. m. on the same day 40 cc. of the same lot of serum diluted with 250 cc. of physiologic solution of sodium chloride was administered over a period of one-half hour. Thirty-five minutes after the injection was completed a reaction occurred which was similar to the first one, but not so severe. The temperature rose from 102 to 102.4 F. and the respiratory rate from 22 to 32. The pulse remained unchanged. After the second injection the patient had an immediate crisis. There was no serum sickness, and recovery from pneumonia was uneventful.

Anaphylactic Reaction.—This type of reaction was characterized by the occurrence of any combination of the following symptoms: itching, urticaria, asthma, angioneurotic edema and laryngeal edema. Reactions presenting these symptoms with or without circulatory changes were included in this class.

Case histories exemplifying the mild and the severe form of this type of reaction follow:

G. P., a 12 year old white boy, had the onset of pneumonia May 23, 1938. He was hospitalized on May 25. Pneumococcus type I was found in the sputum. The personal history was not remarkable except that the patient had received tetanus antitoxin in November 1930; there was no history of allergy. The cutaneous reaction to 0.1 cc. (1:100 dilution) of horse serum was an increase in the size of the wheal with development of pseudopodia and a surrounding area of erythema.

Administration of type I antipneumococcus horse serum was begun on May 27. The data are included in the accompanying tabulation.

Dose	Date	Lot No.	Time Started	Time Completed	Amount of Serum	Amount of Physiologic Solution of Sodium Chloride	Reaction
1	5/27	1 - 50A	12:25 a.m.	12:26 a.m.	0.1 cc.	0	None
2	5/27	1 - 50A	12:45 a.m.	12:50 a.m.	1.0 cc.	0	None
3	5/27	1 - 50A	1:05 a.m.	1:25 a.m.	9.0 cc.	125.cc.	Present

By the time the third injection was completed, flushing of the face had developed, which change was followed by generalized urticaria and itching. Relief was obtained with 0.3 cc. of epinephrine hydrochloride administered subcutaneously. At 1:35 a. m. the patient vomited once and then received 0.7 cc. of epinephrine hydrochloride subcutaneously. The reaction gradually abated, and the patient had completely recovered by 2 a. m.

Administration of serum was then resumed, as follows:

Dose	Date	Lot No.	Time Started	Time Completed	Amount of Serum	Amount of Physiologic Solution of Sodium Chloride	Reaction
4	5/27	1 - 47B	11:00 a.m.	11:30 a.m.	8 cc.	500 cc.	None
5	5/27	1 - 47B	11:13 p.m.	11:25 p.m.	30 cc.	200 cc.	Present

At the end of the fifth injection, the patient complained of itching of the extensor surfaces of the extremities. There were urticarial wheals in this area, which disappeared spontaneously after some minutes. Recovery from pneumonia was uneventful.

M. N., a 5 year old white girl, had the onset of pneumonia May 15, 1938. She was hospitalized May 16. Pneumococcus type I was found in the sputum. The personal history was not remarkable except for the occurrence of purpura two months previously, at which time 3 per cent of eosinophils were found in smears of the peripheral blood. Otherwise there was no history of allergy. There had been no previous administration of serum. The cutaneous reaction to 0.1 cc. (1:100 dilution) of horse serum was a slight increase in the size of the wheal, which was surrounded by an area of erythema 3 cm. in diameter.

Administration of serum was begun at 10 p. m. on May 17, when 0.2 cc. of type I antipneumococcus horse serum (lot 1-50A) was mixed with 2 cc. of physiologic solution of sodium chloride and slowly injected. When the injection was about one-half completed, at 10:01 p. m., the patient complained of itching of the nose and toes, after which complaint she sneezed; then generalized urticaria and marked circumoral pallor developed. The pulse was weak, thready and rapid, although the exact rate was not determined. The rhythm of the pulse was occasionally irregular. The patient felt cold and clammy. There was considerable dyspnea, with a prolonged expiratory phase to the respirations, and the chest was filled with sibilant and sonorous rales. The patient was given 3 minims (0.18 cc.) of epinephrine hydrochloride, and her recovery was complete about one-half hour later.

No further serum therapy was attempted. There was no serum sickness.

Circulatory Reaction.—Any reaction characterized by the occurrence of sudden circulatory changes, such as a rapid, thready or irregular pulse, asystole, "shock," "vascular collapse" (which is sometimes asso-

ciated with coma), profuse cold perspiration, constrictive chest pain, a drop in blood pressure or sudden death, was included in this class, provided that none of the symptoms characterizing the anaphylactic reaction were present. The reactions of all patients with asthmatic symptoms occurring during an immediate reaction were classified as anaphylactic even though in a few instances it seemed fairly evident that this symptom was based on cardiac disease and was the result of acute failure of the left ventricle.[15]

The following records are typical of the mild and the severe form of this type of reaction.

J. C., a 69 year old white man, was seen by his physician six hours after the onset of his disease, on April 15, 1938. Pneumococcus type VIII was found in the sputum. The patient had known of his hypertension for eight to ten years, but had been without symptoms of cardiac disturbance. There was no history of allergy. The patient had never received serum therapy. The cutaneous reaction to 0.1 cc. (1:10 dilution) of horse serum was negative. Administration of serum was begun at 11 p. m. on April 15, when an injection of 40 cc. of type VIII antipneumococcus horse serum (lots 8-04A and 8-05A) was given, at the rate of 1 cc. per minute. During administration of the last 2 cc. of the dose the patient became cyanotic and the pulse was more rapid and felt irregular, weak and thready. Slight dyspnea was also present. There was no urticaria, asthma or chill, and the reaction was not unduly alarming. Ten minims (0.61 cc.) of epinephrine hydrochloride was given, with immediate relief. The patient had an immediate crisis, and no further serum was administered. There was no serum sickness.

D. V., a 58 year old white woman, had the onset of pneumonia May 27, 1938. She was hospitalized May 27. Pneumococcus type V was obtained from the sputum on June 3. There was no history of allergy. It was not known whether the patient had ever received serum previously. There was "myocardial weakness," with moderate dyspnea on exertion. The ophthalmic reaction to 0.1 cc. (1:10 dilution) of horse serum was negative.

Administration of serum was begun on June 3, when 40 cc. of type V antipneumococcus horse serum (lot 357H88J) was injected intravenously, at the rate of about 1 cc. per minute. Near the end of the injection the patient became restless, after which change she suddenly stopped breathing and involuntarily urinated and defecated. It was noted that the patient had become pulseless, and it was thought she had died. One cubic centimeter of epinephrine hydrochloride was given intramuscularly immediately, and the patient responded relatively rapidly. When she became conscious she complained of severe pain in the back. At this time the pulse was weak and thready and there was marked dyspnea, but no asthmatic breathing. The entire reaction was over in about ten minutes. Neither urticaria nor chill was associated with this reaction.

The patient did not have serum sickness, and her recovery from pneumonia was uneventful.

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15. Krehl, L.: Die Erkrankungen des Herzmuskels und die nervösen Herzkrankheiten, Vienna, 1901, pp. 116-120; cited by Pratt, J. H.: Cardiac Asthma, J. A. M. A. **87**:809 (Sept. 11) 1926. Palmer, R. S., and White, P. D.: Clinical Significance of Cardiac Asthma: Review of Two Hundred and Fifty Cases, ibid. **92**:431-434 (Feb. 9) 1929.

Miscellaneous Reactions.—This class included the reactions which were characterized by a variety of minor symptoms but which could not be placed in any of the first three classes. The character and incidence of the various symptoms encountered are listed in table 1. It is possible that further knowledge will permit reallocation of some of the reactions from this heterogeneous class to one of the other classes.

As in most biologic classifications, there were borderline cases, but for the most part the reactions observed fitted easily into the classes described. In this paper, each of the four types, that is, the thermal reaction, the anaphylactic reaction, the circulatory reaction and the miscellaneous reactions, was considered a potential component of any given immediate serum reaction. Some patients were encountered whose reactions presented one component on one injection and a different component on one of the following injections. Occasionally a reaction presented several components on a single injection, for example, the occurrence of urticaria (anaphylactic component) during the serum injection and a chill (thermal component) an hour later.

TABLE 1.—*Character and Frequency of Symptoms Encountered in Patients with Miscellaneous Reactions*

Grouped Symptoms	Frequency
Respiratory (Including dyspnea, cyanosis, choking, change in rate or rhythm of respirations; excluding asthmatic breathing)	02
Precordial (Including pain in precordial region, tightness in chest, substernal pain or pressure; excluding the circulatory reaction)	18
Pulse rate (Including increase or decrease in rate; excluding changes in excursion or rhythm of pulse)	22
Skeletal (Pain in lumbar region of back or in extremities, muscular rigidity)	29
Abdominal (Nausea, vomiting, abdominal pain, desire to defecate)	20
Cerebral (Headache, coma, dizziness, faintness, throbbing of head, blurring of vision)	22
Cutaneous (Including flushing, sensation of heat, perspiration, pallor; excluding urticaria or itching)	15
Total frequency of grouped symptoms	188*

* These grouped symptoms were observed 188 times in 116 patients presenting only a reaction classified here.

In table 2, the character and frequency of simple reactions, those consisting of only one component, are contrasted with the character and frequency of combined reactions, those consisting of two or more components. The occurrence of different components in the reaction to the same injection or to successive injections given the same patient is considered a combined reaction.

ANALYSIS OF THE DATA

A total of 2,340 [16] cases of types I, II, V, VII and VIII pneumococcic pneumonia in which the patients were treated with concentrated type-specific horse serum by intravenous injection were reported from Jan. 1 to Dec. 31, 1938. Immediate serum reactions were observed in 790, or 33.8 per cent, of these cases. The remaining 1,550 cases, in which reactions did not occur, may be considered as a control group. As the definition of an immediate reaction varies widely, it is difficult to compare the total incidence of reactions in this study with that in other published reports.[17]

TABLE 2.—*Distribution of Reactions According to Components Encountered in Individual Patients*

Reaction	Number of Patients		Percentage of Total Number of Patients	
Thermal	218		27.6	
Anaphylactic	130		16.4	
Circulatory	67		8.5	
Miscellaneous	116		14.7	
Simple		531		67.2
Thermal and anaphylactic	50		6.3	
Thermal and circulatory	55		7.0	
Thermal and miscellaneous	92		11.7	
Anaphylactic and circulatory	3		0.4	
Anaphylactic and miscellaneous	16		2.0	
Circulatory and miscellaneous	12		1.5	
Thermal, anaphylactic and circulatory	3		0.4	
Thermal, anaphylactic and miscellaneous	9		1.1	
Thermal, circulatory and miscellaneous	4		0.5	
Anaphylactic, circulatory and miscellaneous	..		...	
Thermal, anaphylactic, circulatory and miscellaneous	..		...	
Combined		244		30.9
Reaction not described		15		1.9
Total number of reactions		790		100.0

The frequency of immediate reactions varied widely with the type of antipneumococcus serum employed (table 3), being highest with type VIII serum (70.2 per cent) and lowest with type I serum (24.3 per cent).

16. This does not include 12 cases in which the details of serum treatment are unknown.

17. (*a*) Bullowa, J. G. M.: The Management of the Pneumonias, New York, Oxford University Press, 1937. (*b*) Finland, M., and Brown, J. W.: Specific Treatment of Pneumococcus Type I Pneumonia, Including Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide, Am. J. M. Sc. **197**:151-168 (Feb.) 1939. (*c*) Brown, J. W., and Finland, M.: Specific Treatment of Pneumococcus Type II Pneumonia, Including Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide, ibid. **197**:369-380 (March) 1939. (*d*) Finland, M., and Brown, J. W.: Specific Treatment of Pneumococcus Type V and Type VII Pneumonias, Including Use of Horse and Rabbit Antipneumococcus Serums and Sulfanilamide, ibid. **197**:381-393 (March) 1939. (*e*) Heffron.[4]

The incidence of reactions in each age group (table 4) was uniform, with the exception of a slightly diminished frequency during the first decade of life, an observation which indicated that age has little effect.

Dilution of serum with physiologic solution of sodium chloride did not appreciably decrease the occurrence of reactions (table 5). Dilution under 1:1 resulted in a somewhat diminished incidence, which, however, was not statistically significant.

TABLE 3.—*Incidence of Immediate Reactions According to Type of Specific Antipneumococcus Serum Given*

Type of Serum Given	Total Number of Patients	Patients with Reaction	Percentage with Reaction
I	1,383	336	24.3
II	231	116	50.2
V	270	69	25.6
VII	251	125	49.8
VIII	205	144	70.2
Total	2,340	790	33.8

TABLE 4.—*Incidence of Immediate Reactions According to Age*

Age Group	Total Number of Patients	Patients with Reaction	Percentage with Reaction
Under 10	289	65	22.5
10 to 19	313	116	37.1
20 to 39	660	227	34.4
40 to 59	716	252	35.2
60 and over	359	129	35.9
Unknown	3	1	....
All ages	2,340	790	33.8

TABLE 5.—*Frequency of Immediate Reactions According to Dilution of Serum with Physiologic Solution of Sodium Chloride*

Ratio of Solution to Serum	Total Number of Patients	Patients with Reaction	Percentage with Reaction
None	518	199	38.4
Under 1: 1	145	41	28.3
1: 1 to 3: 1	226	83	36.7
3: 1 and over	745	258	34.6
"Fixed" dilution*	1,634	581	35.6
"Variable" dilution	706	209	29.6
Total number of patients	2,340	790	33.8

* "Fixed" dilution refers to a constant ratio of solution of sodium chloride to serum in all injections in the treatment of the same patient, in contrast to "variable" dilution, which refers to an inconstant ratio.

ANALYSIS OF REACTIONS IN TERMS OF COMPONENTS

The overlapping of components in some reactions necessitated analysis of the reactions in terms of the total number of components observed. Therefore, the total number of reaction components was greater than the total number of patients in whom the reactions occurred.

The incidence of reaction components tended to vary according to the type of antipneumococcus serum employed (table 6).

Thermal reactions occurred most frequently with the type VIII serum (56.7 per cent) and least often with type V serum (8.5 per cent), although wide variations were noted in the frequency of reactions with any given type, depending on the lot of serum employed. Heffron,[4] in summarizing the literature on the incidence of thermal reactions fol-

TABLE 6.—*Frequency of Reaction Components According to Type of Specific Serum Injected Intravenously*

Reaction Components	Frequency of Reaction Components						Percentage of Components Among Total Number of Patients Receiving Each Specific Type					
	I	II	V	VII	VIII	Total	I	II	V	VII	VIII	Total
Thermal.....	155	71	23	66	116	431	11.2	30.7	8.5	26.3	56.7	18.4
Anaphylactic...	103	38	30	25	15	211	7.4	16.5	11.1	10.0	7.3	9.0
Circulatory.....	51	18	12	31	32	144	3.7	7.8	4.4	12.4	15.6	6.2
Miscellaneous...	106	84	23	49	38	250	7.7	14.7	8.5	19.5	18.5	10.7
Total no. of patients	1,383	231	270	251	205	2,340						

TABLE 7.—*Frequency of Reaction Components According to Age*

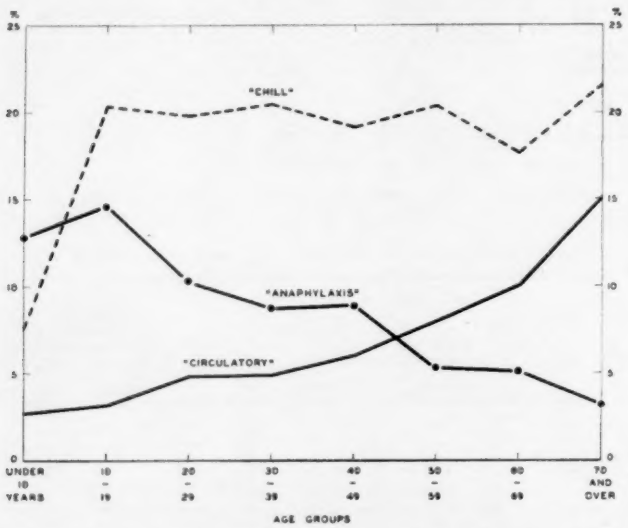
Age Groups	Frequency of Reaction Components				Total Number of Patients	Percentage of Total Number of Patients in Each Age Group According to Reaction Components			
	Thermal	Anaphylactic	Circulatory	Miscellaneous		Thermal	Anaphylactic	Circulatory	Miscellaneous
Under 10.....	22	35	8	13	289	7.6	12.8	2.7	4.5
10 to 19.....	64	46	10	24	313	20.4	14.6	3.2	7.6
20 to 29.....	54	23	13	32	278	19.8	10.3	4.8	11.7
30 to 39.....	80	34	19	45	387	20.5	8.7	4.9	11.5
40 to 49.....	73	34	23	47	379	19.2	8.9	6.0	12.3
50 to 59.....	69	18	27	47	337	20.4	5.3	8.0	13.9
60 to 69.....	42	12	24	24	235	17.7	5.1	10.1	10.1
70 and over.....	27	4	19	18	124	21.6	3.2	15.2	14.4
Age unknown.....	..	..	1	..	3	....	...	....	....
All ages.....	431	211	144	250	2,340	18.4	9.0	6.2	10.7

lowing the use of concentrated antipneumococcus horse serum, indicated that such reactions may occur in 10 to 20 per cent of adult patients. The total incidence of thermal reactions in this series was 18.4 per cent.

Anaphylactic reactions occurred in 9 per cent of all cases. It was not possible to compare this incidence with figures given in the literature because of differences in definition. The occurrence of anaphylactic reactions among the patients in this series varied less from type to type than did that of thermal reactions. The low incidence of anaphylactic reactions in cases of type VIII pneumococcic pneumonia may have depended to some extent on the older age distribution in these cases as compared with that in cases of other types of infection (table 7).[2]

Circulatory reactions were encountered in 6.2 per cent of all the cases (table 6). The high incidence of this type of reaction in cases of type VIII pneumococcic pneumonia (15.6 per cent) also may have depended on the age distribution.

There were striking differences in the age-incidence relations of the various components, as shown in table 7 and the chart. The incidence of thermal reactions in each age group was remarkably constant except that for patients under 10 years of age. The incidence of anaphylactic reactions, on the other hand, decreased as the age of the patients increased. In marked contrast, the incidence of circulatory



Incidence of reaction components among patients in each age group who were treated with intravenous injections of specific antipneumococcus horse serum (types I, II, V, VII and VIII).

reactions took the opposite trend, since the frequency of this type of reaction increases directly with age. The almost perfect uniformity of these two trends in reverse directions was highly significant.

The incidence of a history of allergy (15.5 per cent) and of positive cutaneous reactions (20.2 per cent) among patients having anaphylactic reactions was lower than expected (tables 8 and 9). However, compared with the rates for patients with thermal and circulatory reactions, the frequency of a history of allergy or of positive cutaneous reactions among patients having anaphylactic reactions was approximately twice

as great. If one were to assume that the circulatory reaction represented a degree of protein hypersensitiveness so extreme as to cause a type of reaction in which the circulatory symptoms overshadowed those of asthma and urticaria, one might expect an incidence of positive cutaneous reactions and a history of allergy at least as great as that among those less sensitive patients in whom the reaction was mild enough to allow the symptoms of asthma and urticaria to appear. On

TABLE 8.—*Frequency of Positive History of Allergy According to Reaction Components and Incidence of Reactions*

Reaction Components *	Record of History of Allergy	Positive History of Allergy	Percentage Positive of Recorded Histories
Thermal	368	32	8.7
Anaphylactic	174	27	15.5
Circulatory	112	8	7.1
Miscellaneous	197	19	9.6
Total number of patients with reaction	647	64	9.9
Total number of patients without reaction	1,424	71	5.0
Total number of patients	2,071	135	6.5

* The total incidence of reaction components exceeds the total number of patients with reaction, since a number of the reactions presented more than one component.

TABLE 9.—*Frequency of Positive Cutaneous Reactions According to Reaction Components and Incidence of Reactions*

Reaction of Components *	Record of Cutaneous Test	Positive Cutaneous Reactions	Percentage Positive of Recorded Cutaneous Reactions
Thermal	412	35	8.5
Anaphylactic	203	41	20.2
Circulatory	136	13	9.5
Miscellaneous	235	28	11.9
Total number of patients with reaction	749	87	11.6
Total number of patients without reaction	1,443	67	4.7
Total number of patients	2,192	154	7.0

* The total incidence of reaction components exceeds the total number of patients with reaction, since a number of the reactions presented more than one component.

the contrary, the frequency of a history of allergy or of positive cutaneous reactions among patients having circulatory reactions was of the same order as the frequency among those having thermal reactions, the nature of which generally has been felt not to be on the basis of protein hypersensitivity.[18]

The total number of positive ophthalmic reactions (in 13 of a total of 1,399 tests known to have been performed) was so small as to make

18. (*a*) Sabin, A. B., and Wallace, G. B.: On Nature of Chill-Producing Principle in Antipneumococcus Serum, J. Exper. Med. **53**:339-362 (March) 1931. (*b*) Heffron.[4]

it impossible to determine the significance of the test in a series of patients treated with serum but unavoidably selected so as to remove the more sensitive persons prior to therapy.

An immediate reaction followed the intravenous injection of a test dose of 1 to 2 cc. in only 3 per cent of 366 patients on whom it was known that the test was performed. In spite of this fact, an immediate reaction to at least one of the therapeutic injections following the test dose occurred in 57 per cent of these same patients. Although the arterial blood pressure and pulse rate were not closely observed by the attending physician during injection of most of these test doses, it was the experience at the Albany Hospital, where such observations were made, that the intravenous injection of a test dose was of little value in

TABLE 10.—*Frequency of Preexisting Cardiovascular Disease According to Reaction Components and Incidence of Reactions*

Reaction Components *	Record of Preexisting Complications	Preexisting Cardiovascular Disease †	Percentage of Preexisting Cardiovascular Disease in Recorded Preexisting Complications
Thermal	390	36	9.2
Anaphylactic	192	13	6.8
Circulatory	130	24	18.5
Other	232	22	9.5
Total number of patients with reaction	720	71	9.9
Total number of patients without reaction	1,399	90	6.4
Total number of patients	2,119	161	7.6

* The total incidence of reaction components exceeds the total number of patients with reaction, since a number of the reactions presented more than one component.
† Exclusive of uncomplicated arteriosclerosis.

predicting the occurrence of an immediate serum reaction to a therapeutic dose.

The incidence of circulatory reactions was approximately twice as great as that of thermal reactions and three times as great as that of anaphylactic reactions among patients with a history of preexisting cardiovascular disease, exclusive of uncomplicated arteriosclerosis (table 10). This observation integrates easily with the age distributions of each of the reaction components as previously noted.

The fatality rates of the patients with and of those without reactions were practically the same (table 11).

In relation to the individual reaction components, the fatality rate among those patients having thermal reactions (11.4 per cent) was only two thirds of the rate among patients without reactions (16.4 per cent). This difference was independent of the age factor, since the incidence of thermal reactions was uniform for all age groups, as indicated in table 7. However, the greater frequency of bacteremia among the patients with-

out reaction (19.9 per cent of 607 patients for whom cultures of the blood were made) than among the patients in whom thermal reactions (12.0 per cent of 183 patients) occurred made it impossible to attach any significance to this difference. Heffron and Robinson [19] also found no significant difference in their series of cases of type I pneumococcic pneumonia.

The low fatality rate of the patients having an anaphylactic reaction (10.9 per cent) was most likely related to the high proportion of young persons among those in whom this type of reaction occurred (table 7).

As indicated previously, patients with circulatory reactions had a strikingly high fatality rate (31.9 per cent), twice as high as the patients without such reactions. This was to be expected because of the older age distribution of patients with this type of reaction (table 7), because some of these reactions were fatal in themselves (table 12) and,

TABLE 11.—*Outcome of Pneumonia According to Reaction Components and Incidence of Reactions*

Reaction Components *	Lived	Died	Total	Fatality Rate (Percentage)
Thermal	382	49	431	11.4
Anaphylactic	188	23	211	10.9
Circulatory	98	46	144	31.9
Miscellaneous	212	37	249 †	14.9
Total number of patients with reaction	668	121	789 †	15.3
Total number of patients without reaction	1,296	254	1,550	16.4
Total number of patients	1,964	375	2,339 †	16.0

* The total incidence of reaction components exceeds the total number of patients with reaction, since a number of the reactions presented more than one component.
† Exclusive of 1 patient in whose case the outcome is unknown.

finally, because this group of patients presented the highest incidence of preexisting cardiovascular disease (table 10).

A comparison of the varying degrees of dilution in relation to individual reaction components yielded results similar to those observed in the entire group of patients having immediate reactions (table 5). Dilution was not found to have any effect on the rate of occurrence of any of the reaction components.

The sex of the patient receiving the serum was not a factor in the occurrence of all the immediate reactions or of the individual reaction components. There were approximately 65 per cent males and 35 per cent females in each of the groups comprising the total number of patients, the patients with reactions and the individual reaction components.

The problem of sensitization due to previous injections of serum was not clarified by the evidence at hand, since the majority of patients

19. Heffron, R., and Robinson, E. S.: Final Report of Massachusetts Pneumonia Study and Service 1931-1935, Commonwealth **24**:2 (Jan.-March) 1937.

TABLE 12.—*Data Concerning Patients Whose Deaths During 1937*

Date	Case No.	Type of Pneumonia	Age and Sex	Complications Preceding Pneumonia	History of Allergy	Previous Administration of Serum	Reaction to Horse Serum		Clinical Condition	Lot No. of Serum	Test Dose
							Cutaneous	Ophthalmic			
1937	1	I	22 F	Pregnancy, 7 mo.; miscarriage during pneumonia	None	None	Unknown	Negative	Poor	28A	None
	2	I	75 F	"Cardiac"	None	None	Negative	Negative	Unknown	Unknown	None
	3	I	67 F	Unknown	Negative	Unknown	Negative	Not done	Fair	Unknown	None
	4	I	30 F	Pregnancy, 7 mo.	None	None	Negative	Negative	(?) Poor	40B	1 cc. (N. R.)†
	5	II	80 F	Unknown	None	None	Negative	Not done	Unknown	9B	None
	6	II	53 M	Generalized arteriosclerosis	None	None	Negative	Negative	Unknown	Unknown	None
1938	7	I	62 M	Syphilis of central nervous system; intrinsic asthma, 3 yr.	Eczema and hives in past	None	Negative	Negative	Fair	38B	1 cc. (N. R.)
	8	I	42 F	Obesity; "myocarditis"	None	None	Negative	Not done	Fair	1-45A 1-45B	1 cc. (N. R.)
	9	I	55 M	None	Asthma, 3 to 4 yr.	None	Negative	Negative	Poor	1-47B	1 cc. (N. R.)
	10	II	82 M	Hypertension; cerebral hemorrhage 6 mo. previously	None	None	Negative	Not done	Poor	2-18A*	5 minims (N. R.)

* Ratio of serum to physiologic solution of sodium chloride. † In this table N. R. indicates no reaction.

Total Amount of Serum, Cc.	Amount of Final Dose, Cc.	Number of Injections	Dilution of Final Dose *	Interval, Last Dose to Death	Reaction	Autopsy	Comment
10	10	1	1:1	30 min.	Sudden rapid, weak and thready pulse, becoming imperceptible associated with rapid respiration, at end of injection	None	Acute reaction followed by pulmonary edema and death after 25 min.
40	40	1	1:4	1 hr. 30 min.	Sudden dilatation of pupils; deep cyanosis; rapid and weak pulse; shallow breathing at end of serum administration	None	Artificial respiration and epinephrine hydrochloride necessary to revive patient; condition much worse after reaction, remaining poor until death
80	20	4	Unknown	15 to 20 min.	"Acute cardiac failure"; sudden vascular collapse with no asthma or urticaria	None	Patient moribund on admission, but noticeably improved on morning of fatal injection; no reaction to previous injections
20	19	1	Unknown	1 hr.	Sudden increased cyanosis, associated with weak and irregular pulse; no asthma or urticaria	None	Data somewhat conflicting as to details; death unquestionably related to serum
192	24	4	1:7	30 min.	Sudden circulatory collapse; respiratory standstill and death; no asthma or urticaria	Lobar pneumonia in upper, middle and lower lobes of right lung; congestion and cloudy swelling of viscera	No response to epinephrine hydrochloride; no reaction to previous injections
120	48	2	1:4	7 min.	Sudden circulatory collapse at end of injection with increased cyanosis and dyspnea	Lobar pneumonia in right lung; fibrinous pericarditis; hypertrophy and dilatation of heart; cloudy swelling of liver	
36	35	1	1:5	End of injection	Sudden onset of coughing, dyspnea, asthma and cyanosis	Extreme congestion of blood vessels in kidney; lobar pneumonia; congestion and edema at base of lungs	
100	20	7	1:5	About 3 hr.	Onset of nausea, cloudy vision, cyanosis and dyspnea during injection; pulse rapid and thready; condition poor for 3 hr.; sudden convulsive seizure, followed by death; no asthma or urticaria	Lobar pneumonia in upper lobe of right lung; both lower lobes collapsed; "toxic myocarditis"	No reactions to previous injections
120	20	4	0	End of injection	Color suddenly ashen; two gasps, no pulse, no heart sounds; no response to intracardiac injection of epinephrine hydrochloride	"No cause for sudden death found," only pneumonia and pyoarthrosis in left elbow observed	No reactions to previous injections
5	5	1	0	During injection	Sudden collapse without complaint; color ashen; skin clammy; pulse not palpable; no asthma or urticaria	None	Physician's belief, heart stopped before respirations

TABLE 12.—*Data Concerning Patients Whose Deaths During 1937, 193*

Date	Case No.	Type of Pneumonia	Age and Sex	Complications Preceding Pneumonia	History of Allergy	Previous Administration of Serum	Reaction to Horse Serum		Clinical Condition	Lot No. of Serum	Test Dose
							Cutaneous	Ophthalmic			
	11	II	67 M	"Chronic myocarditis"	None	None	Negative	Negative	Fair	2-21A	1 cc. (N. R.)
	12	II	27 F	Mild hyperthyroidism	None	Diphtheria antitoxin, 17 yr. previously	Negative	Negative	Good	2-13A 2-23B	None
	13	VII	52 M	"Severe cardiac"; had had attacks of decompensation; pneumonia occurred during an attack	None	Unknown	Negative	Negative	Poor	7-06	None
	14	VII	39 F	None	Unknown	Unknown	Not done	Negative	Poor	7-06	4 cc. (N. R.)
	15	VII	68 F	"Chronic myocarditis"	None	None	Negative	Negative	Good	7-06	None
	16	VIII	22 M	Rheumatic heart disease with mitral stenosis and regurgitation	None	None	Negative	Negative	Good	2B	1 cc. (N. R.)
	17	VIII	44 F	Extreme depression due to death in family	None	None	Negative	Negative	Poor	2B	1 cc. (N. R.)
	18	VIII	53 M	None	None	None	Negative	Negative	Good	2B	1 cc. (N. R.)

and 1939 Were "Definitely" Due to Administration of Serum—Continued

Total Amount of Serum, Cc.	Amount of Final Dose, Cc.	Number of Injections	Dilution of Final Dose *	Interval, Last Dose to Death	Reaction	Autopsy	Comment
40	40	1	1:10	2 hr. 45 min.	Chills, cyanosis with labored respirations, considerable dyspnea during injection; deepening of cyanosis; pulse rapid and irregular; failure of patient to rally despite intensive treatment with epinephrine hydrochloride, caffeine, 25 per cent solution of pyridine betacarbonic acid diethylamide (coramine) and oxygen	None	Onset of reaction halfway through projected injection of 75 cc.; injection stopped when about 40 cc. given
55	7	2	1:4	End of injection	Sudden pain in right side of chest associated with peripheral collapse and extreme cyanosis; no asthma or urticaria	None	First dose of 48 cc. given without reaction; patient improving from pneumonia at time fatal dose given; some question whether second dose was necessary
40	40	1	1:12	End of injection	Sudden desire to defecate; death of patient while being placed on bed pan with needle still in vein; no pulse, no heart sound; no asthma or urticaria	None	Complication of cardiac disease and increase of blood volume by injection of 540 cc. of fluid in 40 min.; serum responsible for death according to physician who administered it
70	40	3	0	6 min.	Increase in cyanosis followed by cessation of pulse; respirations rapid; death of patient within 1 min. after onset of reaction	None	Severe pain in back following second dose, only previous reaction
100	40	3	0	20 hr.	Severe dyspnea, almost imperceptible pulse and severe chill at end of injection; temperature rise from 101.8 to 103.2 F.; patient irrational; no recovery from reaction; continuation of weak and thready pulse; no asthma or urticaria	None	Severe lumbar pain, cyanosis, nausea and vomiting after second injection; rise in pulse from 100 to 130; rapid recovery from this reaction, although next injection fatal; no reaction to first dose
40	20	2	1:8	2 hr. 40 min.	Few hives around site of injection at end of injection; no further symptoms until 20 min. later; severe chill followed by rapid respiration, air hunger, rapid and thready pulse, pulmonary edema; course persistently downhill	None	"Patient appeared to die a cardiac death"; no reaction from first injection
40	39	1	0	1 hr. 20 min.	Slight chill followed by circulatory collapse with rapid and thready pulse one hour after injection; death within 20 min.; no asthma or urticaria	None	Patient uncooperative because of mental depression since death of mother 3 wk. previously
40	39	1	0	1 hr. 15 min.	Chill, cyanosis, panting respirations, apprehensiveness, restlessness, stupor, rapid pulse and increasing pulmonary edema 35 min. after injection; condition unchanged for 15 min.; sudden death; no asthma or urticaria	None	Patient in excellent clinical condition; disease mild; reasonable doubt whether serum advisable because of mildness of symptoms

TABLE 12.—*Data Concerning Patients Whose Deaths During 1937, 1938*

Date	Case No.	Type of Pneumonia	Age and Sex	Complications Preceding Pneumonia	History of Allergy	Previous Administration of Serum	Reaction to Horse Serum		Clinical Condition	Lot No. of Serum	Test Dose
							Cutaneous	Ophthalmic			
	19	VIII	75 M	None	None	None	Negative	Not done	Good	8-04	1 cc. (N. R.)
	20	VIII	78 M	Hypertension; arteriosclerotic heart disease with auricular fibrillation	None	None	Negative	Not done	Poor	8-04	None
	21	VIII	81 M	Arteriosclerotic heart disease	None	None	Negative	Negative	Poor	8-04	2 cc. (N. R.)
	22	VI	63 M	Hypertension; cerebral accident, June 1938	None	Unknown	Negative	Negative	Poor	6-01	1 cc. (N. R.)
	23	IV	73 F	Arteriosclerotic heart disease	None	None	Negative	Negative	Poor	4-02	1 cc. (N. R.)
1939	24	II	79 M	"Myocarditis"	Unknown	Unknown	Unknown	Unknown	Unknown	2-25	1 to 2 cc. (fatal)
	25	V	44 F	Rheumatic heart disease with mitral stenosis and insufficiency 6 mo. pregnant; miscarriage, day before onset of pneumonia with retained fragments and severe postpartum bleeding; red blood cells 1,000,000 on admission	Hay fever as a child; none as an adult	None	Negative	Negative	Poor	5-11A	1 cc. (N. R.)

and 1939 Were "Definitely" Due to Administration of Serum—Concluded

Total Amount of Serum, Cc.	Amount of Final Dose, Cc.	Number of Injections	Dilution of Final Dose *	Interval, Last Dose to Death	Reaction	Autopsy	Comment
36	35	1	0	2½ days	Appearance of poor color, rapid and thready pulse, dyspnea and cold and clammy feeling during injection; survived for 2½ days, in poor condition; no recovery from reaction; no asthma or urticaria	None	Physician's belief, serum direct cause of death; pneumonia mild
35	35	1	0	20 min.	Restlessness, suffocation, collapse and death during injection; no asthma or urticaria	None	Physician's belief, death due to an acute cardiac episode
90	40	5	1:4	8 hr.	Sudden collapse with rapid and thready pulse, irregular respirations and coma at end of injection; condition relatively unchanged for 6 hr.; then pulmonary edema and death; no asthma or urticaria	None	Slight chill with labored respirations after second injection; no other reactions
100	99	1	1:1	End of injection	Sudden abdominal pain, rapid, thready and weak pulse and cold and clammy feeling during injection of last few cubic centimeters; pulse increasingly irregular; death within few minutes; no asthma or urticaria	Lobar pneumonia; extreme coronary sclerosis with multiple tiny old healed myocardial infarcts	
100	99	1	1:3	15 min.	Cries because of pain in chest shortly after end of injection; pulse weak and thready; collapse and death in 15 min.; no asthma or urticaria	Lobar pneumonia in middle and lower lobes of right lung; fibrinous pericarditis; anomalous origin of coronary arteries; atheroma of aorta	"Final episode clinically coronary occlusion, coronary spasm or pulmonary embolus"
1-2	1-2	Test dose	0	Few minutes	Deep cyanosis, feeble pulse, asthmatic breathing and death after 1 to 2 cc. injected	None	
95	15	3	1:1	During injection	Sudden death without complaint during injection; sudden stopping of pulse and respirations	None	No reactions to previous injections, but lot no. 5-09 different; patient in poor condition, but sudden death unexpected

who might have had previous injections of serum were those who were immunized against diphtheria. It was impossible to determine in most instances who had received toxin-antitoxin and who had received toxoid (not containing horse serum).

DEATHS ASSOCIATED WITH ADMINISTRATION OF SERUM

During the three year period from Jan. 1, 1937 through Dec. 31, 1939, a total of approximately 5,500 cases in which the patients were treated with concentrated antipneumococcus horse serum were reported to the Bureau of Pneumonia Control. Among these there were 25 deaths (0.45 per cent) which were definitely related to administration of serum. In most instances information regarding fatal reactions was obtained personally from those observing the reaction.

The average age of the patient with a fatal serum reaction was 57.4 years. From 12 of the 25 patients (48 per cent) a history was elicited of preexisting cardiovascular disease exclusive of uncomplicated arteriosclerosis. This was twice the incidence of such disease (23.5 per cent) among all the fatalities in the 2,340 cases in which serum therapy was given from Jan. 1 to Dec. 31, 1938, exclusive of the deaths resulting from serum reactions.

Three of the 25 patients who died were pregnant women (cases 1, 4 and 25), of whom 1 (case 25) also had a history of cardiovascular disease. These pregnant patients were interesting in the light of the demonstrated burden on the circulation imposed by pregnancy and the fact that all were in the sixth or seventh month of pregnancy, when the increase in blood volume due to pregnancy reaches its peak.[20]

A history of allergy was present in only 3 out of a total of 23 cases in which a history was reported as having been taken. One patient (case 7) had a history of eczema and hives. Another (case 9) had had asthma for three to four years previously. A third (case 25) had hay fever during childhood. The allergen in these 3 cases is unknown. Among 19 patients for whom the information was available, there was only 1 (case 12) who had received horse serum previously, the period between injections being seventeen years. A cutaneous test for sensitivity to horse serum was performed in 22 cases, and all reactions were negative. The ophthalmic reaction also was reported as negative in all of the 18 cases in which a test was performed.

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20. Thomson, K. J.; Hirsheimer, A.; Gibson, J. G., Jr., and Evans, W. A., Jr.: Studies on Circulation in Pregnancy: Blood Volume Changes in Normal Pregnant Women, Am. J. Obst. & Gynec. **36**:48-59 (July) 1938. Cohen, M. E., and Thomson, K. J.: Studies on Circulation in Pregnancy: Summary of Studies of Physiolgoy of Circulation of Normal Pregnant Women; New Concept of Nature of Circulatory Burden of Pregnancy and Its Application to Management of Clinical Problems of Pregnancy, J. A. M. A. **112**:1556 (April 22) 1939.

Only 1 (case 24) or possibly 2 (case 7 also) of the fatalities were suggestive of deaths from anaphylactic reaction due to protein hypersensitiveness. In the first instance the patient died after a small dose of serum and had asthmatic breathing as a part of the reaction. Unfortunately, the allergic history and the results of the cutaneous and ophthalmic tests were not available in this case. In the other instance the presence of asthmatic breathing and the past history of eczema and hives were possible indications of protein hypersensitiveness, although the patient had received 80 cc. of serum intravenously without reaction prior to the fatal dose. The possibility that the asthma occurring during this reaction might have been based on cardiac disease must be considered.

During the period in which these deaths from serum reactions occurred, approximately one hundred and five lots of serum were distributed. Nine of the 25 fatalities followed the injection of serum of only three of these lots, each lot being associated with 3 deaths (lots 7-06, 2B and 8-04). The fatal reactions following the use of lot 2B (in cases 16, 17 and 18) were all of the same character, consisting of a chill followed by circulatory collapse, similar to the reaction in the case reported by Cole.[21]

The fatal dose varied in amount from 1 or 2 cc. (case 24) to 99 cc. (cases 22 and 23). Death occurred immediately in some cases, while in case 19 the patient remained in collapse for two and one-half days before death. However, most patients died within one to two hours of the time that the serum was injected.

In 1 instance (case 24) death occurred during the injection of a test dose. In 13 instances death occurred during or after the first therapeutic injection, but in 10 of these the patients previously had received an intravenous test dose without reaction. In the remaining 11 cases the patients died as the result of a therapeutic injection other than the first. Therefore, 21 out of 25 patients had received some serum intravenously without reaction prior to the fatal dose.

The symptoms of the fatal reactions were fairly uniform. Practically all of these patients had vascular collapse. Only 2 (cases 7 and 24) had asthmatic breathing, and only 1 (case 16) had hives. Chills occurred in 5 patients (cases 11, 15, 16, 17 and 18), but in none were they followed by extreme hyperthermia, and all were accompanied by vascular collapse. There was no true death from hyperthermia in this series comparable to those reported in the literature.[22]

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21. Cole, R. I.: Serum Treatment in Type I Lobar Pneumonia, J. A. M. A. **93**:741-747 (Sept. 7) 1929.

22. Conner, L. A.: Experiences in New York Hospital with Treatment of Lobar Pneumonia by Serum-Free Solution of Pneumococcus Antibodies, Am. J. M. Sc. **164**:832-842 (Dec.) 1922. Cecil, R. L., and Larsen, N. P.: Clinical and Bacteriologic Study of One Thousand Cases of Lobar Pneumonia, J. A. M. A. **79**:343-349 (July 29) 1922. Heffron.[4]

TABLE 13.—*Data Concerning Patients Whose Deaths During 193*

Date	Case No.	Type of Pneumonia	Age and Sex	Complications Preceding Pneumonia	History of Allergy	Previous Administration of Serum	Reaction to Horse Serum		Clinical Condition	Lot No. of Serum	Test Dose
							Cutaneous	Ophthalmic			
1937	1	I	55 M	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
	2	I	34 F	Patient moribund	None	None	Negative	Negative	Poor	34-A	1 cc. (N. R.)†
	3	II	67 M	Unknown	None	None	Negative	Negative	Unknown	8	None
	4	II	52 M	Unknown	None	None	Negative	Not done	Moribund	Unknown	3 cc. (N. R.)†
	5	VII	71 F	Unknown	None	None	Negative	Not done	Moribund	2	None
1938	6	I	73 F	Chest tumor of bone density visible in roentgenogram; present at least 3 to 4 yr.; cause of dysphagia and dyspnea	None	None	Negative	Negative	Poor	40-A	None
	7	I	65 M	None	None	None	Negative	Negative	Moribund	40-A	None
	8	I	77 F	None	None	None	Negative	Negative	Poor	1-43A	None
	9	I	72 F	"Myocarditis and nephritis"	None	None	Negative	Negative	Poor	1-46B	None
	10	I	55 F	"Myocarditis," paranoid schizophrenia	None	None	Negative	Negative	Moribund	1-46A	None
	11	II	52 M	None	None	None	Negative	Not done	Moribund	2-18A	None
	12	II	63 M	Hypertension; enlargement of heart	None	None	Negative	Negative	Moribund	2-21D	None

* Ratio of serum to physiologic solution of sodium chloride. † N. R. indicates no reaction.

Total Amount of Serum, Cc.	Amount of Final Dose, Cc.	Number of Injections	Dilution of Final Dose *	Interval, Last Dose to Death	Reaction	Autopsy	Comment
80	40	2	Unknown	Unknown	Death from "cardiac collapse" 1½ hours after final injection of serum started	None	No reaction to either injection indicated; no further data obtainable
120	30	3	1:1	2 min.	"Evidence of respiratory failure followed by cardiac failure"	None	Seven day interval between second and third doses; repeated cutaneous and ophthalmic reactions negative at time of fatal injection; patient moribund; relationship of serum to death difficult to decide
155	15	3	1:5	Unknown	Circulatory collapse from last 2 doses; clinical diagnosis, coronary occlusion	Bronchopneumonia in right lung; healed myocardial infarction; acute aortic endocarditis with infarcts in lungs, spleen and kidneys	
43	40	1	Unknown	30 min.	Death shortly after administration of serum; coma, cyanosis and imperceptible pulse present before serum given	None	Physician unable to decide whether serum a factor in death
10	10	1	Unknown	About 1 hr. 30 min.	Chill during injection, followed by dilatation of pupils, stiffness of joints, "skipping heart"	None	Relation of reaction to death difficult to decide
40	26	2	Unknown	3 days	Deep cyanosis, frothing at mouth at end of second injection; "almost died"	None	Condition not as good after serum reaction; survival for 3 days; physician unable to decide relation of serum reaction to death
60	20	2	0	11 min.	Administration of serum a "desperate measure" for moribund patient; after injection pulse more rapid and weak, cyanosis deeper, respirations shallower; no asthma or urticaria	None	Physician's belief, patient "dying," perhaps serum shortened life by few hours
70	20	4	1:75	40 min.	Sudden onset of pulmonary edema with rales at bases of both lungs; fall in blood pressure; increase in pulse; death	None	Physician's impression, too rapid increase in blood volume was cause of death; death not related to serum itself (1,500 cc. injected in approximately 1 hr. in a woman 77 years old)
20	20	1	0	5 min.	"No serum reaction"; "patient was dying; her heart became weaker after serum injection and she died 5 min. later"	None	Impossible to decide whether serum caused death of patient with terminal disease
20	20	1	0	Few minutes	Rolling of eyes few minutes after injection of serum; pulse more thready; respirations unchanged; no asthma or urticaria	None	Patient practically dead at time serum was administered; impossible to determine whether death would have occurred a few hours or minutes sooner if serum had been omitted
110	30	2	0	10 min.	Irregular shallow breathing; cessation of pulse and then of breathing during second injection	None	Deep cyanosis, sterterous breathing, coma and weak pulse several hours before injection
144	48	3	1:3	End of injection	Weak and irregular pulse, deep cyanosis and "early circulatory collapse before injection," increased severity of symptoms during injection; death at end of injection	None	Impossible to decide whether serum made death occur sooner than expected

TABLE 13.—*Data Concerning Patients Whose Deaths During 1937, 193*

Date	Case No.	Type of Pneumonia	Age and Sex	Complications Preceding Pneumonia	History of Allergy	Previous Administration of Serum	Reaction to Horse Serum		Clinical Condition	Lot No. of Serum	Test Dose
							Cutaneous	Ophthalmic			
	13	V	70 M	Arteriosclerotic heart disease; angina pectoris	None	None	Negative	Negative	Moribund	0-05B	None
	14	V	44 M	None	None	None	Negative	Negative	Poor	5-05A	None
	15	VIII	40 F	Unknown	Unknown	Unknown	Negative	Negative	Moribund	8-03A	None
	16	VIII	44 M	None	None	None	Negative	Negative	Moribund	Unknown	None
	17	VIII	7 F	None	None	None	Negative	Not done	Moribund	8-04	1 cc.
1939	18	I	60 F	None	None	Antipneumococcus horse serum, Feb. 1938	Negative	Negative	Poor	1-58A	1 cc. (N. B.)†
	19	I	80 M	None	None	None	Negative	Negative	Poor	1-59A	None
	20	I	16 M	Rheumatic heart disease	None	Unknown	Negative	Negative	Fair	1-57A	None
	21	IV	45 M	Chronic alcoholism	Unknown	Unknown	Negative	Negative	Poor	4-04	None
	22	IV	88 M	None	None	None	Negative	Not done	Poor	4-04	None

and 1939 Were "Possibly" Due to Administration of Serum—Concluded

Total Amount of Serum, Cc.	Amount of Final Dose, Cc.	Number of Injections	Dilution of Final Dose *	Interval, Last Dose to Death	Reaction	Autopsy	Comment
60	10	2	1:14	During injection	Patient moribund; sudden death during injection when about ¾ of projected dose given	None	Physician's impression, death not related to serum in spite of occurrence during administration, since patient in terminal stage
40	40	1	1:12	Unknown	Impossible to state; data inconsistent	None	No data available beyond moribund condition of patient and death during injection
40	40	1	1:4	1 hr. 30 min.	Severe chill followed by cyanosis, shallow breathing, rapid and thready pulse and delirium	None	Although reaction severe, patient moribund; attending physician unwilling to state reaction caused death, willing to concede it might have shorted life by an hour or two
40	40	1	0	10 hr.	Slight chill, weakness, restlessness, temperature rise from 100 to 106 after reaction, pulse more rapid and weak; pulmonary edema	None	Patient thought to be moribund; physician's belief, life may have been shortened by a few hours
1	1	Test dose	1:8	20 min.	Patient moribund with almost imperceptible pulse at time of injection; patient slightly worse after injection of serum	Resolving pneumonia; purulent pericarditis	Physician's impression, patient dying; perhaps death hastened by administration of serum
120	60	3	1:⅛	10 min.	Patient moribund at time of administration of last dose; difficult to decide whether slight change in pulse after administration of serum was due to serum	None	No reactions to previous injections; normal ecg. at time of admission to hospital; in second ecg. taken after second dose changes were consistent with acute coronary thrombosis, although patient had no symptoms; patient progressively worse up to time of final injection
40	20	2	1:5	3¼ hr. 15 min.	"Circulatory collapse" after second dose, but patient very ill and physician doubtful that change due to serum	None	Exact relationship between administration of serum and death difficult to establish because of age and condition of patient; no reaction to first injection
40	20	2	1:25	13 hr.	Two hours after serum, chill, dyspnea and cyanosis followed by massive hemoptysis; profuse perspiration followed by rapid pulse; patient gradually worse till time of death	None	Physician doubtful whether reaction fatal in patient without severe rheumatic heart disease; intravenous injection of 500 cc. of fluid in patient with cardiac disease also a possible factor; no reaction from first injection
35	35	1	1:¼	2 hr. 40 min.	Momentary cessation of breathing; injection stopped; after intravenous injection of epinephrine hydrochloride consciousness regained, accompanied by severe chest pain; gradually recovered from reaction; condition worse later; death	None	Physician's belief, death due to cardiac failure and not to administration of serum
20	20	1	1:1	1 hr. 15 min.	Some muscular twitching of arms and neck with rolling of both eyes and rigidity of neck; administration of serum stopped; clearing of acute symptoms; patient very ill; death 1 hr. and 15 min. after serum injected	None	Serum a possible factor in death, according to administering physician

Among those cases in which an autopsy was performed, the observations were variable. No one change was characteristic of all, except the presence of the pneumonia. The ballooning of the lungs due to acute emphysema, reported in about one half of the autopsy protocols collected by Sheppe,[23] was not observed in any of the autopsies in this series. In most of Sheppe's cases, however, there was definite evidence of protein hypersensitivity prior to the fatal reactions. Moon [24] expressed the belief that the pathologic changes in acute anaphylactic shock were uniform, although his definition of human anaphylaxis was vague.

In table 13, *22* cases are tabulated in which death occurred during or shortly after the administration of serum. However, other complicating factors existed, making it impossible to decide whether serum was implicated in the death of the patients. Most of the patients were moribund at the time of the administration of serum and died during or shortly after the injection. The deaths were felt by the attending physicians not to be the result of serum therapy, although a few of these cases are but slightly different from those included in table 12.

COMMENT

Thermal Reactions.—The results of this study in relation to thermal reactions coincide with those in the literature in that this type of reaction appears to depend on the lot of serum used.[25] However, the host factor cannot be entirely dismissed, since even the worst chill-producing lots do not cause chills in every case. Another consideration regarding thermal reactions is the route of injection of the serum. Intravenous administration is much more likely to cause such reactions than is intramuscular or subcutaneous administration.[26]

Although there is definite evidence that the process of concentration of serum has reduced thermal reactions,[18] additional factors must be considered. It is well known that laboratories producing serum may concentrate pooled serums from the same horses by the same method in two separate lots, one lot of which may be reaction free, while the other may produce severe chills. Moreover, the unconcentrated serum itself may be reaction free, while the concentrated product of the same

23. Sheppe, W. M.: Fatal Anaphylaxis in Man, J. Lab. & Clin. Med. **16**:372-379 (Jan.) 1931.

24. Moon, V. H.: Pathology and Mechanism of Anaphylaxis, Ann. Int. Med. **12**:205-216 (Aug.) 1938.

25. Leys, D.: Observations on Serum Treatment of Type I Lobar Pneumonia, Lancet **2**:748-751 (Sept. 30) 1933. Cecil, R. L., and Sutliff, W. D.: Treatment of Lobar Pneumonia with Concentrated Antipneumococcus Serum, J. A. M. A. **91**:2035-2042 (Dec. 29) 1928.

26. Cecil, R. L., and Baldwin, H. S.: Treatment of Lobar Pneumonia with Subcutaneous Injections of Pneumococcus Antibody Solution, J. Pharmacol. & Exper. Therap. **24**:1-12 (Aug.) 1924. Kereszturi, C., and Hauptman, D.: Serum Treatment of Pneumonia in Children, J. Pediat. **4**:331-341 (March) 1934.

serum may produce chills.[18a] This difference may be due to the concentration of a hypothetic chill-producing substance or to the introduction of such a substance during the process of concentration. The relationship of these chill-producing substances to the pyrogenic substances in solution of sodium chloride [27] also needs clarification.

Anaphylactic Reactions.—The data presented in this paper suggest that the host factor in relation to age, incidence of a history of allergy and positive cutaneous reactions is of primary importance in the occurrence of this type of reaction, in contradistinction to the importance of the serum factor among the patients who had thermal reactions.

The most probable reason for the rarity of severe anaphylactic reactions in this series lies in the selection of patients for treatment. It is evident that there must have been patients with pneumonia from whom serum therapy was withheld because of a history of hypersensitivity to horse hair, dander or serum, a strongly positive cutaneous or ophthalmic reaction or a history of recent administration of serum. Indeed, physicians often have reported verbally that a patient did not get serum for one of these reasons. If serum is withheld from such patients, no report of that fact is made to the Department of Health, and therefore the size of this group of untreated patients cannot be determined. Of all of the 2,340 cases reported in 1938, there was not one in which a history of specific allergy to horse hair or horse dander would indicate susceptibility to anaphylactic reactions to horse serum.[28] In considering the data in this paper, this weeding out of the sensitive patients must be kept in mind.

Circulatory Reactions.—This type of reaction seems about equally dependent on the host and on the serum factor. The host factor is important in relation to the age of the patient and the history of preexisting cardiovascular disease, while the relation to the serum factor is demonstrated in table 12, in which groups of deaths from this type of reaction are related to certain lots of serum.

The literature contains reports of cases and deaths which appear to have been associated with this type of reaction, although the reaction was usually reported as anaphylactic. Billings [29] stated that in the care-

27. Hort, E. C., and Penfold, W. J.: The Dangers of Saline Injections, Brit. M. J. **2**:1589 (Dec. 16) 1911. Co Tui and Schrift, M. H.: Production of Pyrogen in Sera by Bacteria, Proc. Soc. Exper. Biol. & Med. **42**:549 (Nov.) 1939.

28. Ratner, B., and Gruehl, H. L.: Anaphylactic Crossed Relationship Between Horse Dander and Horse Serum, Arch. Path. **8**:635-644 (Oct.) 1929. Ratner, B.: Possible Explanation for Horse Serum Anaphylaxis in Man, J. A. M. A. **94**:2046-2050 (June 28) 1930.

29. Billings, F., in discussion on Park, W. H.: Is Serum Anaphylaxis a Danger of Sufficient Importance to Limit Our Use of Protective Sera in the Treatment or Prevention of Disease? Tr. A. Am. Physicians **28**:95-102, 1913.

ful administration of polyvalent antistreptococcus serum to 25 patients, "three patients nearly died of collapse" after 10 cc. of refined serum had been injected. In a report of the Therapeutic Trials Committee of the Medical Research Council,[30] the statement was made that the administration of a few "batches" of serum resulted in "general collapse with feeble pulse," which reaction was considered "toxic rather than anaphylactic," but no data regarding these reactions were published. Waldbott,[5a] in an addendum to a report of 9 deaths from anaphylactic shock, described a typical fatal circulatory reaction which had been reported verbally to him and expressed the belief that it was different from the reactions reported in his paper and that it was due to "embolism." Moon [24] published a case report of a death due to "anaphylaxis" in a patient who showed no evidence of any type of sensitivity prior to the fatal injection; he assumed the death was related to "sensitized endothelium" of the capillaries. In that case the symptoms of a circulatory reaction were present. Bullowa [17a] published a report of 8 cases in which death was due to serum reactions, in at least 5 of which the description was that of a circulatory reaction. Heffron [4] also reported 2 deaths from reactions which fit into this category.

The general impression resulting from a review of the literature is that all injections of protein materials resulting in death or in severe reactions other than thermal reactions are automatically called "anaphylactic" whether or not there is any evidence of hypersensitivity. A recent case report [31] in which the patient did not present a shred of evidence of hypersensitivity is typical of that point of view. If the injected material is nonprotein in nature, the term "anaphylaxis" is not so likely to be used. Hanzlik and Karsner [32] have shown that severe reactions can occur in animals from the injection of nonprotein as well as protein materials without any relation to hypersensitivity and have termed these reactions "anaphylactoid." It would seem more logical to approach the problem from the point of view that there are many varieties of reactions that can occur after the intravenous injection of foreign substances and that the anaphylactic type of reaction is but one of these.

The evidence in this paper does not indicate that anaphylactic reactions cannot occur. It does indicate, however, that fatal anaphylactic reactions are rare if proper precautions are observed. This opinion is

30. Report of the Therapeutic Trials Committee of the Medical Research Council: The Serum Treatment of Lobar Pneumonia, Lancet **1**:290 (Feb. 10) 1934.

31. Ziskind, J., and Schattenberg, H. J.: Fatal Anaphylactic Shock in Man, Arch. Int. Med. **62**:813-820 (Nov.) 1938.

32. Hanzlik, P. J., and Karsner, H. T.: Anaphylactoid Phenomena from Intravenous Administration of Various Colloids, Arsenicals and Other Agents, J. Pharmacol. & Exper. Therap. **14**:379 (Jan.) 1920.

in agreement with that of Park.[33] On the other hand, the fact that anaphylactic reactions can be kept at a minimum in a series such as this does not mean that other types of fatal serum reactions will not occur. The deaths following serum reactions reported in this paper indicate that fatal reactions do occur in the absence of known or detectable sensitivity. Moreover, evidence is presented that particular caution must be used in the administration of serum to elderly patients or to patients with cardiovascular disease. This evidence is not in agreement, therefore, with the recent report of the Committee on Sensitization and Reactions of the American Drug Manufacturers Association,[34] which, in a comment on Bullowa's reported cases of fatal reactions [17a] that did not appear to be related to protein hypersensitivity, stated "There are factors which make it questionable if the serum was in any way responsible for the deaths."

If the cases of death reported in this paper are compared with those compiled by Lamson,[3a] striking differences are apparent. The clinical picture of reaction in most of his cases is similar to that classified as anaphylactic in this paper, but quite different from that of the fatal reactions herein reported. Most of his patients were young persons who had been treated for diphtheria with serum injected intramuscularly, and most of them had a striking history of allergy and severe reactions to small amounts of injected serum. In the present series the patients were much older and received treatment for pneumonia with large amounts of serum injected intravenously. The severe reactions occurred in persons without a demonstrable sensitivity and were mostly circulatory in nature.

The evidence presented in this paper demonstrates fairly conclusively that circulatory reactions are not related to recognizable protein hypersensitivity, although the exact mechanism of this type of reaction is unknown.

Neither are circulatory reactions associated with the rapid intravenous introduction of fluids ("speed shock"),[35] since the rate of injection of the serum was carefully checked in those patients suffering from this type of reaction and did not exceed 1 to 2 cc. per minute in practically all cases. Moreover, the use of the "slow continuous intravenous drip method" [36] in a considerable proportion of the patients treated did not prevent the occurrence of these reactions.

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33. Park, W. H.: Antitoxin in Diphtheria, J. A. M. A. **76**:109 (Jan. 8) 1921.

34. Report of Committee on Sensitization and Reactions, American Drug Manufacturers Association, Am. Drug Manufacturers Proc., 1939, p. 243.

35. Hirshfeld, S.; Hyman, T. H., and Wanger, J. J.: Influence of Velocity on the Response to Intravenous Injections, Arch. Int. Med. **47**:259 (Feb.) 1931.

36. Hyman, T. H., and Hirshfeld, S.: Technic of Intravenous Drip, J. A. M. A. **96**:1221-1223 (April 11) 1931.

The most pertinent leads in the study of the mechanism of such reactions lie in certain observations on the specific effect of serum and other injected substances on the cardiovascular system. If protein decomposition products are present in certain lots of concentrated antiserum, the theory postulated by Cannon [37] for traumatic shock may be operative. This possibility is being explored. The injection of horse serum in dogs not previously sensitized to it changes the permeability of the pulmonary capillaries,[38] and the injection of defibrinated blood from a foreign species results in a sharp decrease in the coronary blood flow of the isolated heart-lung preparation of the dog.[39] In patients with pneumonia it has been demonstrated [40] that significant changes in the electrocardiogram occur during therapeutic intravenous injections, including those of antipneumococcus horse serum, even when no reactions occur. Further studies are being conducted in the hope of interpreting such changes in relation to the class of immediate serum reactions known as circulatory.

CONCLUSIONS

An analysis of data concerning a large series of patients treated with concentrated type-specific antipneumococcus horse serum by intravenous injections demonstrates that their immediate serum reactions can be grouped into three definite classes, thermal, anaphylactic and circulatory, and a fourth miscellaneous class.

That the distinction between circulatory and anaphylactic reactions is not artificial is indicated by the striking differences in the symptoms of the reactions, the age distributions and the incidence of positive histories of allergy, positive cutaneous reactions and preexisting cardiovascular disease.

A series of fatal serum reactions is reported and analyzed. Most of the fatalities followed the occurrence of a circulatory reaction.

Serious anaphylactic reactions following intravenous serum therapy are shown to be infrequent in the experience of physicians in the state of New York.

The various factors affecting the incidence of the different types of immediate reactions are discussed in the light of published data on serum reactions in man.

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37. Cannon, W. B.: Traumatic Shock, New York, D. Appleton and Company, 1923.

38. Sherwood, N. P., and Stoland, O. O.: Anaphylaxis: Pulmonary Permeability in Normal and Sensitized Dogs and Its Relation to Anaphylactic Shock, J. Immunol. **20**:101-115 (Feb.) 1931.

39. Katz, L. N.; Weinstein, W., and Jochim, K.: Coronary Vasoconstrictor Action of Foreign Species Blood, Am. Heart J. **15**:452 (April) 1938.

40. Rutstein, D. D.; Thomson, K. J.; Tolmach, D. M., and Floody, R. J.: Electrocardiographic Changes During Intravenous Therapy of Pneumonia, J. Clin. Invest. **19**:780-781 (Sept.) 1940.

TORULA INFECTION OF THE LUNGS AND CENTRAL NERVOUS SYSTEM

REPORT OF SIX CASES WITH THREE AUTOPSIES

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Torula infection is recognized as a rare disease caused by a yeastlike parasitic fungus belonging to the fungi imperfecti which seems to have a special predilection for the central nervous system and lungs. Cryptococcus hominis has recently come into rather general use as the name for the pathogenic organism of this disease.

According to Freeman,[1] Zenker's report in 1861 of a case in which involvement of the central nervous system occurred probably represents the first description of torula infection in man. As early as 1901 Vuillemin [2] first used the term C. hominis for the yeastlike organism found in the lesions of European blastomycosis. Frothingham,[3] studying a tumor-like mass in the lung of a horse in 1902, discovered and described the yeastlike fungus causing the lesion. After cultural examinations and animal inoculations, he concluded the pulmonary lesion in the horse was caused by a torula. There seems little doubt the fungus he isolated was the organism now known as Torula histolytica.

In Germany von Hansemann [4] and Türk,[5] in 1905 and 1907, respectively, each reported a case of so-called blastomycosis involving the central nervous system in human beings. In this country Rusk and

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Read before the Academy of Neurological Surgery, Oct. 22, 1940 at Cleveland.

From the Departments of Surgery (Neurologic) and Pathology of the University of Southern California and the Good Hope Clinic Hospital Association.

1. Freeman, W.: Torula Infection of the Central Nervous System, J. f. Psychol. u. Neurol. **43**:236 (Nov.) 1931.

2. Vuillemin, P.: Rev. gén. de sc. pures et appliq. **12**:732, 1901.

3. Frothingham, L.: A Tumor-Like Lesion in the Lung of a Horse Caused by Blastomyces (Torula), J. M. Research **9**:31, 1902.

4. Von Hansemann, D.: Ueber eine bisher nicht beobachtete Gehirnkrankung durch Hefen, Verhandl. d. deutsch. path. Gesellsch. **9**:21, 1905.

5. Türk, W.: Ein Fall von Hefeinfektion (Saccharomykose) der Meningen, Arch. f. klin. Med. **90**:335, 1907.

Farnell [6] reported 2 cases of "systemic oidiomycosis" in 1911 and 1912 which have been considered due to Torula.

As a result of their comprehensive monograph in 1916, Stoddard and Cutler,[7] differentiated torulosis properly from other, similar mycotic infections involving the central nervous system and applied the term T. histolytica to the organism. In so doing, they isolated the fungus by cultural methods, studied it further by animal inoculations and histologic sections and accurately described the clinical characteristics of the disease. They added, moreover, 2 cases to the others previously described. Since that time several comprehensive articles have been published, among them those of Freeman and Weidman [8] in 1923, Sheppe [9] in 1924, Stone and Sturdivant [10] in 1929, Freeman [1] in 1931, Levin [11] in 1937 and Longmire and Goodwin [12] in 1939.

Unfortunately, not only has the term "blastomycosis" been used for different mycoses caused by unrelated species of fungi, but undoubtedly different terms have been applied to infections produced by the same fungus. This confusion has been aggravated by the somewhat uncertain state of the terminology of these fungi. Because of the important work of Benham [13] in 1934, however, doubt concerning the identical nature of the fungus described earlier by Busse and Vuillemin and T. histolytica was removed. Benham [14] studied and compared the reactions and characteristics of C. hominis (Busse and Vuillemin) with those of T. histolytica and found them identical in every respect. Inasmuch as the generic term Cryptococcus (Kützing) em Vuillemin is commonly applied by medical mycologists to fungi imperfecti which appear only as round or oval cells reproducing by budding, she concluded that the

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6. Rusk, G. Y., and Farnell, F. J.: Systemic Oidiomycosis, Univ. California Publ. Path. **2**:47, 1912.

7. Stoddard, J. L., and Cutler, E. C.: Torula Infection in Man, Monograph 6, Rockefeller Institute for Medical Research, 1916.

8. Freeman, W., and Weidman, F. D.: Cystic Blastomycosis of the Cerebral Gray Matter Caused by Torula Histolytica Stoddard and Cutler, Arch. Neurol. & Psychiat. **9**:589 (May) 1923.

9. Sheppe, W. M.: Torula Infection in Man, Am. J. M. Sc. **167**:91 (Jan.) 1924.

10. Stone, W. J., and Sturdivant, B. F.: Meningo-Encephalitis Due to Torula Histolytica, Arch. Int. Med. **44**:560 (Oct.) 1929.

11. Levin, E. A.: Torula Infection of the Central Nervous System, Arch. Int. Med. **59**:667 (April) 1937.

12. Longmire, W. P., Jr., and Goodwin, T. C.: Generalized Torula Infection: Case Report and Review with Observations on Pathogenesis, Bull. Johns Hopkins Hosp. **64**:22 (Jan.) 1939.

13. Benham, R. W.: The Fungi of Blastomycosis and Coccidioidal Granuloma, Arch. Dermat. & Syph. **30**:385 (Sept.) 1934.

14. Benham, R. W.: Cryptococci, J. Infect. Dis. **57**:255 (Nov.-Dec.) 1935; footnote 13.

disease resulting from these rudimentary fungi should be classified under the cryptococcoses and, in view of priority, the name given by Vuillemin, C. hominis, should be retained for this organism.

Not uncommonly it will be found that the protean nature of the clinical manifestations of cryptococcosis has in many instances caused the disease to be confused with tuberculous meningitis, epidemic encephalitis, syphilis and tumor or abscess of the brain. Frequently, moreover, the cause has been revealed only at the time of necropsy. That the diagnosis of torulosis may continue to be difficult and confusing is indicated by the following reports of cases of this unusual condition.

REPORT OF CASES

CASE 1.—*History.*—L. L. M., a 25 year old Filipino cook, entered the Los Angeles County Hospital Aug. 26, 1931 complaining of headache, stiffness of the neck, backache and vomiting during the previous ten days. It was also learned that about two or three weeks prior to admission he was at times confused and irrational. During the preceding three months he had complained of a sore throat. His family and past histories were found to be without significance.

Examination.—The patient seemed drowsy and appeared ill. The temperature was 99.8 F., the pulse rate 60 and the respiratory rate 22. The tonsils were not enlarged, but there was some injection of the pharynx. Pyorrhea alveolaris was noticeable. The neck was stiff on forward movement. No cervical adenopathy was noted, and nothing unusual was discovered in the heart, lungs or abdomen. The Kernig and Brudzinski signs were positive on the right and left side. The Babinski and allied signs were also positive bilaterally. No other neurologic findings were recorded at this time.

Roentgenograms of the paranasal sinuses and chest disclosed nothing unusual. A blood count made at the time of admission showed 16,700 leukocytes, with 68 per cent polymorphonuclear leukocytes. A lumbar puncture revealed a slightly cloudy fluid which was under a pressure of 28 mm. of mercury and contained 315 cells per cubic millimeter, among which the polymorphonuclear leukocytes predominated. Culture of the fluid showed no growth and no acid-fast organisms. The fluid from a lumbar puncture the following day was cloudy and contained 1,860 cells, 86 per cent of which were polymorphonuclear leukocytes and the remainder small lymphocytes. The Pandy reaction was positive. Again, the culture showed no growth, and there was no evidence of acid-fast organisms.

The Wassermann reactions of both the blood and the spinal fluid were negative.

Stiffness of the neck, diplopia in all directions and recent choking of the optic disks, with overfilling of the vessels, were noted in the examination on September 2. The deep reflexes of the lower extremities were more hyperactive on the right side than on the left, and although the Babinski and allied signs were positive bilaterally, they were more strongly positive on the right side than on the left. Tuberculous meningitis was thought the most likely diagnosis at this time.

Daily lumbar punctures were performed. The cell count varied from 400 to 3,000 per cubic millimeter of spinal fluid. The pressure of the spinal fluid increased gradually, being reported over 400 mm. of fluid after September 13. On September 12 the content of sugar in the spinal fluid was 19 mg., of chlorides 673 mg. and of total protein 660 mg. per hundred cubic centimeters. Cultures

continued to be sterile, and no acid-fast bacilli were found. It was not until September 15 that torulas were discovered in the spinal fluid. This identification was confirmed by the department of mycology.

Course.—The patient continued to be irrational and drowsy. After September 2 right hemiparesis gradually developed, and the choking of the optic disks became more apparent. Bilateral paresis of the sixth nerve also became evident at this time. His temperature varied between 100 and 101 F., except on two occasions, when it was 104 F. Unfortunately, at his death, on Sept. 21, 1931, permission for autopsy was refused.

CASE 2.—*History.*—E. P., a 36 year old white man, a laborer, was in good health until March 6, 1933, when he experienced severe frontal headaches. Some three days later he vomited several times and thereafter was distressed by nausea and vomiting. He continued working but fainted on two occasions a few days prior to hospitalization at the Los Angeles County General Hospital. With the onset of his illness he was at times confused and complained also of dimness of vision. The day prior to admission his neck was stiff and his back painful. He had also felt feverish at times and drowsy. The family and past history as obtained revealed nothing of consequence.

Examination.—The patient was roused with some difficulty. The temperature was 100.2 F., the pulse rate 60, the respiratory rate 18 and the blood pressure 124 systolic and 76 diastolic. Nothing noteworthy was discovered in the general physical examination. Examination of the cranial nerves revealed equal but slightly irregular pupils which reacted sluggishly to light. Although his visual acuity was markedly diminished, this could not be tested accurately because of his illness. The fundi showed blurring of the margins of the disks, with overfilling of the veins. Partial left homonymous hemianopia was also described. Nothing abnormal was reported in the remaining cranial nerves. Except for a bilaterally positive Kernig sign, the general neurologic examination revealed nothing remarkable.

Roentgenograms of the chest and skull made March 24 disclosed nothing unusual. On admission the leukocyte count was 11,800, with 80 per cent polymorphonuclear leukocytes. Lumbar puncture revealed a pressure of 250 mm. of spinal fluid, which was slightly cloudy. The cell count was 770, and 84 per cent of this number were polymorphonuclear leukocytes. The Pandy reaction was negative. The impression at this time was that of tuberculous meningitis.

A lumbar puncture the following day showed pus cells and budding yeastlike bodies on the smear. No growth was obtained on culture. A subsequent lumbar puncture revealed a pressure of 375 mm. of spinal fluid, which was slightly cloudy and contained 590 cells. The Gram stain showed many small, gram-positive, round objects, some of which appeared to be budding. A study of the fluid by the department of mycology led to the identification of T. histolytica. The patient's condition became rapidly worse, and he died March 25.

Autopsy.—The calvarium appeared normal. The pia-arachnoid showed diffuse and moderate opacity, the thickening being most marked along the superficial vessels and sulci. In some places small, discrete tubercles were present along the blood vessels. The convolutions of the brain were moderately flattened, slightly more on the right side than the left. The pial surfaces were congested, and in many places there were small hemorrhages. Many small hemorrhages were found on the left frontal operculum. At the base of the brain were small collections of exudate in the sulci and the basilar cisterns. The middle ears, mastoid cells and accessory nasal sinuses revealed no inflammatory changes.

The lungs were hyperemic and moderately edematous. No bronchopneumonia or granulomatous lesions were found. Except for slight arteriosclerotic involvement of the coronary arteries, the heart appeared normal. The liver weighed 1,720 Gm., and the various cut surfaces revealed cloudy swelling. The spleen was slightly softened and enlarged, weighing 240 Gm. The other organs examined disclosed nothing grossly abnormal.

Microscopic Examination.—In the brain a marked increase in the number of interstitial cells was noted in the subcortical white matter. These cells were also more numerous in the deeper layers of the cortex. The subarachnoid space was loaded with inflammatory exudate, which consisted of round cells and fewer polymorphonuclear leukocytes. Yeast cells were found in large numbers free in the exudate and within large phagocytic cells. No lesions due to Torula were found in the other organs examined histologically.

CASE 3.—*History.*—M. S., a 25 year old white man, was well until about two months prior to admission to the Los Angeles County Hospital on April 9, 1933, when he complained of nausea and vomiting. About two weeks prior to hospitalization, the onset of fever and constant, severe frontal headache occurred and he noticed blurred vision. He gave no history of unconsciousness, convulsions or incontinence. The family and past histories were noncontributory.

Examination.—The patient responded slowly to questioning and complained of severe headache. The neck was slightly stiff in forward movement. Otherwise nothing unusual was discovered in the general physical examination.

The neurologic examination as recorded revealed external deviation of the left eye. The pupils were round, regular and equal. They responded poorly to light. Examination of the remaining cranial nerves and the general neurologic examination disclosed nothing noteworthy.

Roentgenograms of the paranasal sinuses, chest and skull revealed nothing unusual. The erythrocyte count was 4,100,000 and the leukocyte count 7,150, with 84 per cent neutrophils. An initial pressure of over 400 mm. of spinal fluid was obtained on lumbar puncture. The cell count was 227 per cubic millimeter, with 14 per cent polymorphonuclear leukocytes and 86 per cent lymphocytes. No organisms were seen on the smear, and no growth was obtained on culture. The Wassermann reactions of both the blood and the spinal fluid were negative.

Daily lumbar punctures were performed. The pressure was invariably high and the cell count between 100 and 300 per cubic millimeter. The smears continued to show no organisms and the culture no growth. It was not until April 15 that fluid obtained by cisternal puncture revealed a few cells and yeastlike bodies on the smear. Cultures yielded the same organisms, which were identified as T. histolytica by the department of mycology.

Course.—The patient failed to improve and remained restless and irrational. The temperature varied between 99 and 101 F. He was taken home, against advice, April 30 and died a few weeks later. Permission for an autopsy was not obtained.

CASE 4.—*History.*—A. C. L., a girl aged 15 years, was seen in consultation with Dr. Robert L. Cunningham at the Hospital of the Good Samaritan, Los Angeles, June 16, 1938. Her present illness began in India in August 1937 with headache, nausea and vomiting. At times her vision became blurred, and on some occasions she saw double. She also noticed some stiffness of the neck. During this time she had a slight fever and some morning cough, raising sputum.

After the onset of her illness, she was taken to the Carmichael Hospital for Tropical Diseases at Calcutta, India, at which time a palpable spleen was noted.

Nothing unusual was discovered in the neurologic examination. She had a leukocyte count of 10,200 per cubic millimeter, with 68 per cent polymorphonuclears. Results of tests for undulant fever were reported as negative. Lumbar puncture revealed fluid under moderate pressure. It was clear but showed a few cells with the lymphocytes predominating. Azosulfamide (the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonic acid) was given parenterally with no noticeable improvement.

Two months after the onset of her symptoms a roentgenogram of the chest revealed interlobar empyema on the right side, and for this reason she was operated on October 30. An examination of the pus showed no organisms, and the culture was reported as sterile. The material removed at operation consisted mainly of fibrous tissue, with signs of chronic inflammation.

A second lumbar puncture on Dec. 2 showed a pressure of 290 mm. of spinal fluid. The smear revealed a fairly large number of polymorphonuclear cells but no organisms, and the culture was sterile. At this time the Wassermann reaction of the spinal fluid was reported as positive and the Wassermann reaction of the blood as doubtfully positive. Roentgenograms of the skull revealed a beaten-silver appearance with the convolutional markings greatly increased. On Jan. 1, 1938 dimness of vision was first noticed, more pronounced in the right eye. On ophthalmologic examination the optic disks were pale, particularly that of the right eye.

On February 7, with the use of avertin with amylene hydrate and local anesthesia, a right frontal craniotomy was performed. The dura was opened and the brain found to be under increased pressure, but no evidence of an abscess was discovered. Subsequent to this procedure, she was free of vomiting and headache for about three weeks, after which the symptoms gradually recurred. Her postoperative convalescence was otherwise essentially uneventful. Ophthalmoscopic examination March 8 showed considerable progression of the optic atrophy in each eye. Because this seemed primary and the Wassermann reactions were positive, syphilis was believed to be the cause. The family and past histories, however, were not significant.

The patient returned with her mother to California, their previous home, April 23. Although her general condition improved during the trip, she had a slight rise in temperature in the afternoon and fatigued easily; the chest sinus continued draining.

Examination.—Examination at the Hospital of the Good Samaritan revealed an apathetic, pale and rather emaciated white girl of 15 years, weighing about 80 pounds (36.3 Kg.). Her temperature was 98.6 F., her pulse rate 108 and her respiratory rate 22. A well healed right frontal craniotomy scar was evident; associated with this was a small decompression, which was not under pressure. The head was freely movable in all directions, without stiffness of the neck. Inspection of the chest revealed a drainage site in the region of the second right interspace anteriorly in which an iodoform wick was present. With the exception of dulness over the right upper part of the chest, the percussion note was resonant throughout, and no rales were heard. There was no precordial enlargement; the heart sounds were clear and regular, and no murmurs were heard. The abdomen and extremities were not remarkable.

Examination of the cranial nerves revealed definite pallor of both optic disks, more pronounced on the right than on the left. The appearance was that of primary optic atrophy. The pupils were found to be circular and equal, though somewhat dilated. They reacted sluggishly to light but well in accommodation. The extraocular movements were normally performed. Examination of the other cranial nerves disclosed nothing abnormal. The visual fields appeared slightly constricted to rough testing. The patient was not well enough for a perimetric examination.

In view of her general weakness, the motor power of the extremities was not significantly lessened. Sensation was intact throughout, and tests for coordination gave normal results. The deep and superficial reflexes were equal and active; the Babinski and allied signs, negative. The blood pressure was 120 systolic and 80 diastolic.

Roentgenograms of the chest on June 16 revealed an area of density extending outward and slightly upward from the right hilus. This density lay entirely in the anterior part of the chest, and part of it appeared to involve the interlobar fissure. There was no evidence of a cavity or fluid level within this density, and the rest of the pulmonary field was clear (fig. 1). Roentgenographic study of the skull showed the presence of the right frontal craniotomy wound, which was well healed, without evidence of infection of the bone. The sella was a little

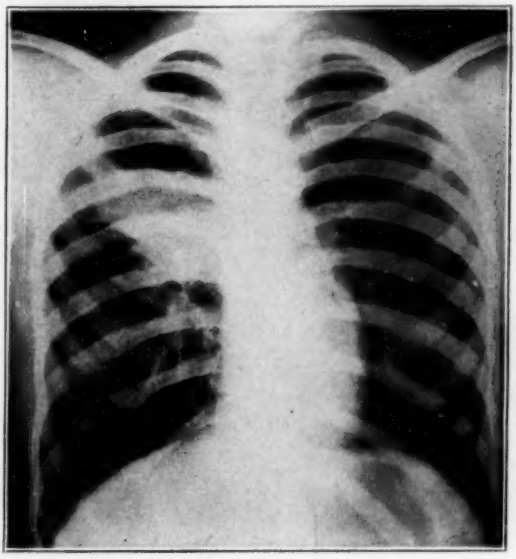

Fig. 1 (case 4).—Roentgenogram of the chest taken June 16, 1938.

larger than normal but revealed no evidence of erosion. The convolutional markings were considerably accentuated.

Urinalysis disclosed nothing abnormal. Examination of the blood revealed a hemoglobin content of 67 per cent, an erythrocyte count of 4,010,000, a leukocyte count of 7,100, with 65 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes, 7 per cent monocytes and 1.5 per cent eosinophils, and a negative Wassermann reaction of the blood. A lumbar puncture June 17 registered a pressure of 200 mm. of spinal fluid, which was slightly cloudy, contained 73 cells per cubic millimeter, with polymorphonuclears predominating, and showed 175 mg. of protein per hundred cubic centimeters. The Wassermann reaction of the spinal fluid was negative, but the colloidal gold curve was 5555554211.

Some of the purulent fluid was aspirated from the draining sinus in the chest. Microscopic examination of a wet mount preparation showed numerous polymorpho-

nuclear leukocytes and numerous round, double-contoured bodies, surrounded by a clear zone, resembling T. histolytica (fig. 2). Gram stain of a smear revealed numerous polymorphonuclear leukocytes and a moderate number of gram-positive, yeastlike bodies. T. histolytica was grown in culture.

A second examination of the spinal fluid on June 23, with the removal of about 8 cc. of slightly cloudy fluid, revealed 92 cells per cubic millimeter, 16 per cent polymorphonuclear leukocytes and 84 per cent lymphocytes. Cultures made from the centrifuged material produced a growth of T. histolytica. Injection of this material into mice produced the characteristic lesions of Torula (fig. 3), and typical colonies were again grown from the material taken from these lesions.

The patient was discharged from the hospital June 25, and returned to her home in Pomona, Calif. She was given 15 grains (0.97 Gm.) of potassium iodide daily.

Fig. 2 (case 4).—Photomicrograph of an unstained wet mount preparation of material from the discharging chest sinus. The mucinoid envelop is seen as a clear zone or halo surrounding each organism. × 500.

Second Admission.—She was admitted March 29, 1939 to the Hospital of the Good Samaritan through the Good Hope Clinic for reexamination and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) therapy. Whereas previously she weighed 80 pounds (36.3 Kg.), her weight was now 97 pounds (44 Kg.) (fig. 4). Until January 1939 she suffered occasionally with headaches, after which they no longer occurred. She realized her vision had improved and that she felt stronger. Although her chest continued draining, she was no longer troubled with coughing. She also commented on the fact she felt much more alert mentally. During September 1938 her periods, which had ceased during her illness, returned and remained regular.

At this time it was found she could not read with her right eye, but could count fingers at a distance of 1 foot (30 cm.). With her left eye she was able

to read the headlines of a newspaper. The results of neurologic examination were otherwise essentially unchanged. Stereoroentgenograms of the chest and a right lateral projection disclosed that the abnormal density springing from the right hilus, noted previously, had shrunken in all diameters.

A cell count of 87, showing 34 per cent polymorphonuclears, 65 per cent lymphocytes and 1 per cent eosinophils, was found on examination of the spinal fluid. A wet mount preparation from the centrifuged specimen revealed no yeastlike bodies.

Fig. 3 (case 4).—Photomicrograph of a section of mouse lung. The mouse died after an intraperitoneal inoculation of the cerebrospinal fluid from the patient in case 4. Hematoxylin and eosin stain; × 500.

Cultures of the same, however, disclosed a few colonies of T. histolytica. Material taken from the chest sinus contained numerous yeast cells. T. histolytica grew on culture mediums.

On March 30 the patient was given 20 grains (1.29 Gm.) of sulfapyridine four times daily, which dosage was changed to 15 grains (0.97 Gm.) five times daily on March 31. A concentration of sulfapyridine of between 9 and 13 mg. per hundred

cubic centimeters of blood was maintained. This treatment was continued until her discharge from the hospital April 8.

Third Admission.—She was readmitted to the hospital May 16, with evidence of further improvement. The drainage from the chest had become less profuse. Examination gave essentially the same results as previously, except that she seemed stronger and more alert. The neurologic findings were essentially unchanged. The visual fields were charted; although she fatigued easily, with a large object the left field was outlined fully, while the right showed a large and somewhat irregular defect over most of the temporal area.

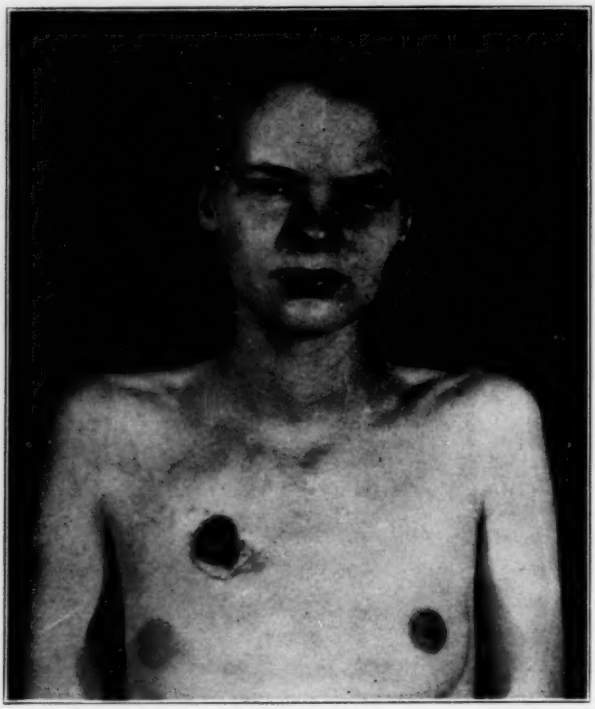

Fig. 4 (case 4).—Photograph of the patient during her second admission to the hospital, March and April 1939. The sinus in the right side of the chest is plainly visible, and the healed scar of the craniotomy in the center of the forehead is also apparent.

Roentgenograms of the chest and the results of fluoroscopic observation May 18, when compared with those last made, showed that the triangular area running upward and outward from the right hilus was much smaller. Nothing suggesting new spread or reinfection was seen.

Numerous pus cells and a moderate number of torulas were present in the exudate from the chest sinus. Lumbar puncture showed a pressure of 250 mm. of spinal fluid, with 117 cells per cubic millimeter and a total protein content of

350 mg. per hundred cubic centimeters. She was given 20 grains (1.29 Gm.) of sulfanilamide four times daily, which maintained a concentration of sulfanilamide of 9 to 12 mg. per hundred cubic centimeters of blood. She tolerated her treatment well and was discharged May 26.

Fourth Admission.—She was readmitted December 16. She had gained about 15 pounds (6.8 Kg.), so that her weight on this admission was 113 pounds (51.3 Kg.). She stated that the chest sinus was smaller and was certain she had gained in strength, mentioning that she could walk a mile (1.6 kilometers) without tiring. Her periods continued to be regular. Her vision was essentially unchanged. Examination disclosed a decrease in the size of the chest sinus with less evidence of granulation tissue. The patient appeared more alert. Charting revealed no change in the visual fields.

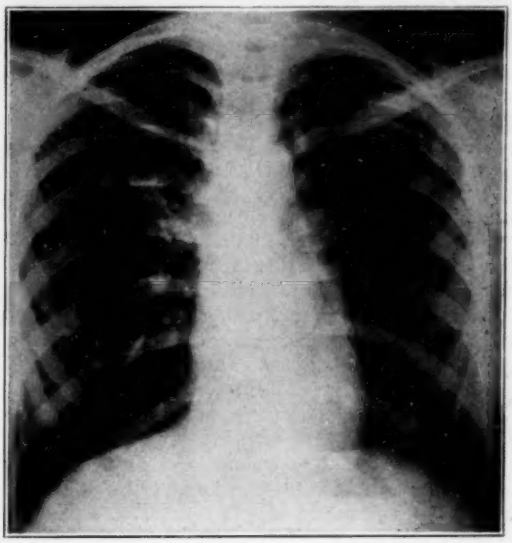

Fig. 5 (case 4).—Roentgenogram of the chest Dec. 18, 1939. The improvement in the condition of the chest is readily apparent.

Roentgenograms and fluoroscopic examination of the chest showed that there had been a remarkable decrease in the amount of density of the upper field of the right lung, there being only a small amount of residual fibrotic-appearing density at the level of the second rib anteriorly near the hilus (fig. 5). A lumbar puncture disclosed a pressure of 200 mm. of spinal fluid, which was clear and colorless, with a cell count of 46 per cubic millimeter. The total protein was 225 mg. per hundred cubic centimeters. No organisms were observed in a wet-mount preparation of the centrifuged sediment, but a few colonies of torulas were obtained on Sabouraud's medium.

On December 16 she was given 0.1 cc. by intradermal injection and 0.1 cc. by subcutaneous injection of undenatured torula antigen 1 (Krueger). On December 19, 0.1 cc. was given by intradermal injection and 0.2 cc. by subcutaneous injection.

On December 23, an injection of 0.1 cc. was given intradermally and of 0.3. cc. subcutaneously. She tolerated the treatment well and was discharged December 23, to continue taking potassium iodide. She has remained about the same since that time. Fluid obtained by lumbar puncture April 17, 1940 contained 66 cells per cubic millimeter, had a total protein content of 140 mg. per hundred cubic centimeters, showed no organisms on microscopic examination and yielded only 2 colonies of T. histolytica on 2 dextrose agar slants and a dextrose agar plate.

Case 5.—*History.*—B. M. M., a 52 year old laborer, entered the Santa Fé Hospital Jan. 28, 1938 complaining of dull frontal headache of six weeks' duration. This followed a cold, which had cleared up in a few days. The headaches persisted and gradually became more severe. He was able to continue working until two weeks prior to hospitalization, when there developed general malaise, night sweats, fever and some drowsiness.

Examination.—The patient was rather drowsy and appeared ill. The temperature was 99 F., the pulse rate 82, the respiratory rate 20 and the blood pressure 160 systolic and 110 diastolic. Otherwise the general physical examination revealed nothing unusual. A neurologic examination was not recorded, but it was observed that his pupils were equal and active and the Babinski reaction negative.

Examination of the blood on January 29 revealed a hemoglobin content of 105 per cent; an erythrocyte count of 5,210,000; a leukocyte count of 17,300, with 92 per cent polymorphonuclear leukocytes and 8 per cent lymphocytes; a negative Wassermann reaction of the blood, and a culture negative after forty-eight hours. A cell count of 46 per cubic millimeter, with lymphocytes predominating, was found on examination of the spinal fluid. The Pandy reaction was negative and the sugar content normal. No organisms were found. Another puncture two days later revealed 23 cells, with a normal content of globulin and sugar. On this occasion both the smear and the culture showed the presence of yeast cells. Yeast cells were also found in the smears and cultures on six subsequent examinations of the spinal fluid. The cell counts of these specimens varied from 190 to 300 mm. per cubic millimeter. The fungus found in the spinal fluid was identified as T. histolytica.

The patient's condition failed to improve, and he died February 22. His temperature varied between 99 and 104 F., with an average of 100 to 101 F. He was given azosulfamide parenterally, without beneficial effect, and remained irrational and stuporous most of the time.

Autopsy.—An autopsy was performed by the coroner's department and the brain examined by Dr. C. B. Courville. Except for slight widening of the sulci in some areas, the convolutions of the brain appeared normal. Close inspection of the leptomeninges disclosed a peculiar mottled appearance, which seemed due to an unusual striation of fibrinous reticulum in the subarachnoid space. This reticulum was formed of tiny nodules, some no larger than a pinpoint. This was noted particularly over the frontal lobes. A few small nodules were found around the basilar surface of the cerebellum. Sections of both cerebral hemispheres disclosed a small isolated spot in the basilar cortex on the left side. In the right hemisphere another small lesion, measuring about 2 by 1.5 cm., was found in the external capsule. The ventricles were lined with granulation tissue. Sections through the cerebellum and brain stem failed to disclose any additional lesions.

Microscopic Examination.—Many lymphocytes, a few polymorphonuclear leukocytes and numerous yeast cells were present in the pia-arachnoid spaces of the

brain. Microscopic examination of the bone marrow, lungs, kidneys, spleen and liver showed no evidence of torula infection.

CASE 6.—*History.*—B. C. M., a 24 year old mechanic, entered the Los Angeles County Hospital Sept. 19, 1939 complaining of vomiting and occipital headaches during the preceding week. About two months prior to hospitalization he noticed a small furuncle on his left wrist, which persisted for about two weeks. It was

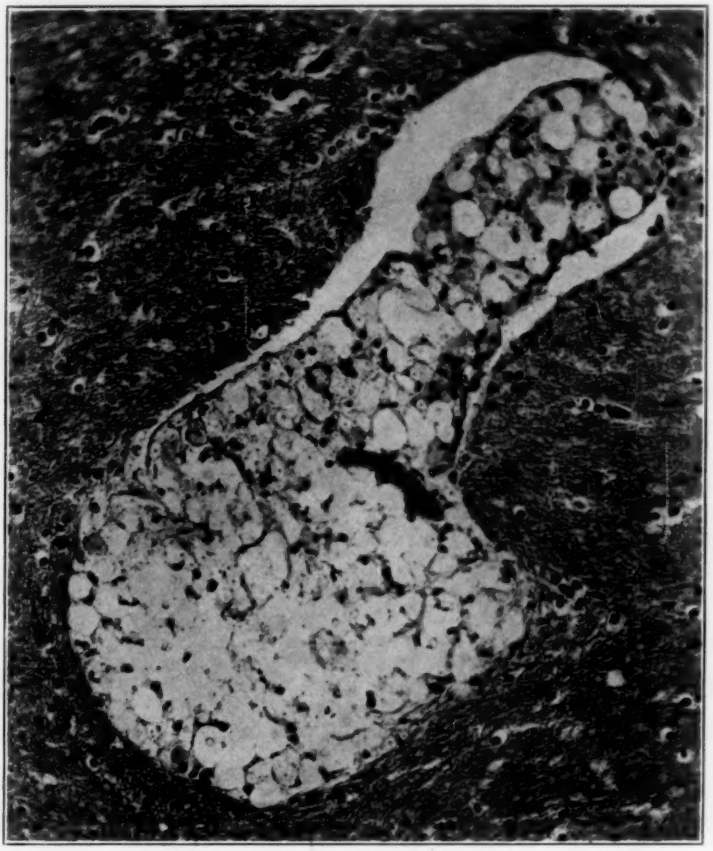

Fig. 6 (case 6).—Photomicrograph of torulas in the meninges. × 230.

also stated that he coughed up reddish brown sputum a few days before his entry, but none thereafter. The family and past histories were without significance.

Examination.—The patient complained of severe headache and appeared ill. His neck was stiff. Except for a slight systolic murmur at the apex, nothing unusual was discovered on examination of the chest, and the rest of the physical examination disclosed nothing remarkable. A complete neurologic examination was not recorded, but it was noted that he had slight weakness of the left side of the face,

his deep reflexes were noticeably diminished and the Babinski sign was negative bilaterally. On admission it was believed the patient had meningitis, possibly tuberculous.

A pressure well over 400 mm. of spinal fluid was found on entry. The cell count was 235 per cubic millimeter; the chlorides measured 690 mg. and the total protein 72 mg. per hundred cubic centimeters. Microscopic examination of

Fig. 7 (case 6).—Photomicrograph of a giant cell containing torulas in the spleen. × 345.

the sediment revealed numerous yeast buds morphologically resembling T. histolytica. This diagnosis was confirmed by culture of the spinal fluid.

Roentgenograms of the chest disclosed nothing pathologic. The Wassermann reactions of both the blood and the spinal fluid were negative. Daily spinal punctures disclosed similar high pressures and cell counts, ranging between 100 and 500 per cubic millimeter. Torulas were found on all smears and cultures. The

patient was given sulfanilamide, the concentration of which in the blood was maintained between 10 and 20 mg. per hundred cubic centimeters. Three days prior to his death, on November 29, this was changed to sulfapyridine. His course was progressively downhill. A postmortem examination was made and the brain examined by Dr. C. B. Courville.

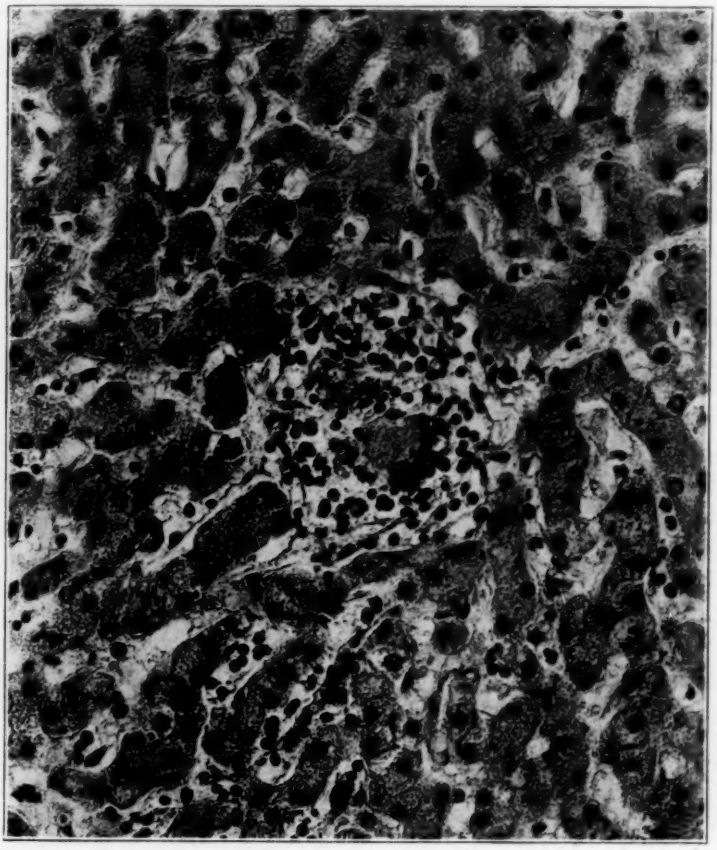

Fig. 8 (case 6).—Photomicrograph of a tubercle and giant cell containing torulas in the liver. × 345.

Autopsy.—The convolutions of the brain were somewhat flattened. Small accumulations of exudate were found in the sulci. In one place tubercles were discovered at the base of the brain along the vessels. There was some herniation of the cerebellar tonsils.

The heart was normal in appearance and weighed 300 Gm. A few small hemorrhages were found in the pleura. The parenchyma of the lungs was moder-

ately congested, hemorrhagic in places and free of granulomatous lesions. The liver weighed 2,200 Gm. The markings and color were within normal limits. The weight of the spleen was 900 Gm. The follicles were enlarged. The pulp was firm and dark red. The kidneys together weighed 390 Gm. and were normal except for congestion and parenchymatous degeneration.

Microscopic Examination.—Brain: Varying amounts of granulation tissue and round cell infiltration containing small and large yeast cells were seen in the pia-arachnoid space (fig. 6). In some areas the yeast cells were present in large numbers, around which there was little tissue reaction. Budding was noticed in many of the cells. Just below the pia a few poorly defined tubercles containing many yeast cells were found. Deeper within the brain substance the granulomatous process involved some of the Virchow-Robin spaces. One section of the cervical portion of the cord presented the same histologic picture as that in the pia-arachnoid space. In this section one tubercle was found deep within the white matter.

Other Organs: There was a definite increase of reticulum of the spleen and an occasional siderosclerotic nodule. In a few isolated areas yeast cells were found in giant cells and free in the pulp (fig. 7). The pulp in places was diffusely infiltrated with varying numbers of polymorphonuclear leukocytes, round cells and eosinophils. The kidneys were interesting in that a number of glomerular tufts contained small areas of necrosis, in which yeast cells were found. In a section of an adrenal gland two small tubercles with central areas of necrosis contained yeast cells. Similar lesions in small numbers were found in the sections of the liver (fig. 8). The section of a lung revealed a few areas of hemorrhage involving the air spaces, thickened alveolar walls infiltrated with small numbers of polymorphonuclear leukocytes and round cells. In some of the thickened alveolar walls giant cells containing yeast bodies were found. We believe this case represents another example of generalized torula infection.

All of the organisms in these 6 cases were identified by culture and animal inoculation by Dr. John F. Kessel, of the department of mycology of the Los Angeles County Hospital. He also reproduced torula meningitis in monkeys with each of the cultures.

DIAGNOSIS AND CLINICAL PICTURE

As was previously intimated, not only may the antemortem diagnosis of torula infection be difficult, but frequently it is not made. The first 2 cases reported by Cutler and Stoddard were in Dr. Harvey Cushing's service at the Peter Bent Brigham Hospital. As mentioned by Cushing, in a discussion on a paper by Shapiro and Neal,[15] in both there were symptoms of intracranial pressure without localizing features, operation was without avail and the diagnosis was made only at autopsy. In his 60 collected cases, Levin [11] found the condition diagnosed prior to death in 37 instances and at autopsy in 23 instances.

Often the onset of the disease is insidious with intermittently severe frontal headaches, but not infrequently it may be sudden with headaches more pronounced and associated with spells of vomiting. Dizziness, vertigo and stiffness and pain in the back of the neck are not uncommon

15. Shapiro, L. L., and Neal, J. B.: Torula Meningitis, Arch. Neurol. & Psychiat. **13**:174 (Feb.) 1925.

symptoms, and visual disturbances, such as amblyopia, diplopia, strabismus, nystagmus and ptosis, are also reported rather frequently. Mental symptoms, including confusion, drowsiness, restlessness and delirium, have been described commonly. Ataxia and hemiplegia have also been noted.

The commonest physical symptom has been stiffness of the neck, with positive Kernig and Brudzinski signs. Fever, if present, is of only moderate degree, and the leukocyte count is usually not much elevated. Neuroretinitis and papilledema are frequently seen. The reflexes have been variably reported. Occasionally the Babinski sign is obtained. Although occasional periods of remission have been noted, the course of the disease is usually downhill, and the patient ultimately becomes comatose and dies of respiratory failure. If the lungs are involved, the clinical picture may suggest tuberculosis or tumor. There is usually a cough, some pain in the chest, malaise and loss of weight, but little or no fever or night sweats.

In the cases reviewed by Levin,[11] it is interesting to discover that prior to culture or autopsy, tuberculous meningitis was diagnosed in 10 instances, undesignated meningitis in 5, encephalitis in 7, tumor and abscess of the brain in 6 and 4, respectively, and psychotic dementia in 5. He reported involvement of the central nervous system alone in 30 cases and of the lungs in 9 cases and generalized involvement in 8 cases.

One to six months has been the usually recorded duration of the disease. In Levin's [11] series of 60 cases, however, he found the duration of the illness to be one month or less in 3 cases, two months in 10, twenty-five to thirty mnoths in 5 and six years in 1.

PORTAL OF ENTRY

In most instances the respiratory tract has been considered the route by which the cryptococcus enters the body. Freeman and Weidman [8] suggested the tonsils as a portal of entry. Some have expressed the opinion that the parasite gained entrance by way of the gastrointestinal tract. In a case reported by Johns and Attaway [16] the initial lesion was found to be a small superficial granuloma which developed from a razor cut and resulted in meningitis, with characteristic organisms in the cerebrospinal fluid.

INCIDENCE

In 1925 Shapiro and Neal [15] collected a total of 15 cases of torula infection, including 1 of their own. In 1930 Freeman [17] reviewed the

16. Johns, F. M., and Attaway, C. L.: Torula Meningitis: Report of Cases and Summary of Literature, Am. J. Clin. Path. **3**:459 (Nov.) 1933.

17. Freeman, W.: Torula Meningo-Encephalitis: Comparative Pathology in Nineteen Cases, Tr. Am. Neurol. A. **56**:203, 1930.

gross and histopathologic changes observed in 19 cases of torulosis and in his monograph in 1931 [1] reported a total of 43 cases. Since that time Levin [11] found 15 more which, with the 2 he reported in 1938, brought the total to 60 cases of invasion of the central nervous system by Torula. Including the cases recently reported by Taber,[18] Caldwell,[19] Crone,[20] Quodbach,[21] Cudmore and Lisa,[22] de Busscher and his associates,[23] Greenfield, Martin and Moore,[24] Longmire and Goodwin,[12] Magruder,[25] D'Aunoy and Lafferty [26] and Robertson and his associates,[27] together with our cases reported here, the total number is now 79. In view of the early misleading reports on the identity of such fungous infections, however, one is forced to be somewhat hesitant about accepting the accuracy of the number of these cases reported in the literature to date, but their occurrence has at all events been relatively uncommon.

CLASSIFICATION AND DIFFERENTIATION OF THE BLASTOMYCETES

Similarity of the characteristics and activities of the fungi comprising the blastomycetes requires some consideration of their differentiating features. It should be stated, however, that none of the numerous classifications proposed has been generally adopted and any discussion of the classification of the yeasts and molds is open to criticism. In this group cryptococcosis, or torula infection, blastomycosis, or oidiomycosis, and coccidioidal granuloma are the ones most apt to be confused. The saccharomycetes, or true yeasts, involve the skin usually to a mild extent only; the monilia attacks the mucous membranes, mouth, gastrointestinal

18. Taber, K. W.: Torulosis in Man, J. A. M. A. **108**:1405 (April 24) 1937.

19. Caldwell, G. T.: Systemic Cryptococcosis with Report of Case, Texas State J. Med. **33**:310 (Aug.) 1937.

20. Crone, J. T.; DeGroat, A. F., and Wahlin, J. G.: Torula Infection, Am. J. Path. **13**:863 (Sept.) 1937.

21. Quodbach, K.: Ein Beitrag zur Pathologie der Blastomykose der Zentralnervensystems, Zentralbl. f. allg. Path. u. path. Anat. **69**:227 (Feb. 20) 1938.

22. Cudmore, J. H., and Lisa, J. R.: Torula Meningo-Encephalitis: A Case Report, Ann. Int. Med. **11**:1747 (March) 1938.

23. de Busscher, J.; Scherer, H. J., and Thomas, F.: La méningite à Torula (contribution à l'étude des localisations nerveuses des infections à pseudolevures), Rev. neurol. **70**:149 (Aug.) 1938.

24. Greenfield, J. A.; Martin, J. P., and Moore, M. T.: Meningo-Encephalitis Due to Cryptococcus Meningitidis (Torula Histolytica), Lancet **2**:1154 (Nov. 19) 1938.

25. Magruder, R. G.: Torula Infection of the Central Nervous System: Three Cases, J. Lab. & Clin. Med. **24**:495 (Feb.) 1939.

26. D'Aunoy, R., and Lafferty, C. R.: Torula Meningitis in Child, Am. J. Clin. Path. **9**:236 (March) 1939.

27. Robertson, W. E.; Robertson, H. F.; Riggs, H., and Schwartz, L.: Torulosis Involving the Human Cerebrum, J. A. M. A. **113**:482 (Aug. 5) 1939.

tract, lungs and intertriginous portions of the skin, while C. hominis, Oidium dermatitidis and Coccidioides immitis frequently involve the central nervous system. In the case of the mycoses due to the last two organisms, however, invasion of the nervous system is usually secondary to or associated with involvement elsewhere, particularly of the skin or subcutaneous tissues.

The similarity of C. hominis to O. dermatitidis and C. immitis invariably requires differentiation of these fungi by means of morphologic characteristics, cultural reactions and animal inoculation, in which case the identity can be established with certainty. Although the methods of distinguishing these fungi and the differences in their pathologic picture are interesting and important phases of mycology as related to C. hominis, it was not considered within the scope of this article to review this subject, which is so well discussed in such standard texts as those of Zinsser and Bayne-Jones [28] and Gay.[29]

The importance of examination, culture and animal inoculation of the spinal fluid in cases of obscure cerebrospinal diseases, especially those characterized by severe headache without a definite cause, becomes readily apparent.

MORPHOLOGIC AND CULTURAL CHARACTERISTICS

The cells of the pathogenic torula measure from 1 to 13 microns in diameter. Budding, which constitutes their only method of reproduction, is invariably evident, the buds having thinner walls than the mother cell, the walls of which may be highly refractile. Surrounding the organisms in the tissues there is practically always a clear zone composed of gelatinous material, which constitutes a characteristic feature of the lesion and which caused Stoddard and Cutler to name the parasite T. histolytica. The organism itself is surrounded by a thick capsule of mucoid material. In artificial cultures the morphologic characteristics are practically the same except that no capsules are formed. Within the cells may be seen numerous granules, many of which are composed of a fatty material, as shown by the sudan III stain. In sections the cells stain irregularly, but a thick wall is usually visible.

The artificial growth of Torula consists of forms practically identical with those seen in the tissues, having no resemblance to molds and consisting of yeastlike budding organisms. Gelatin shows only slight liquefaction after six or eight weeks, and no gaseous fermentation of the sugar occurs. On the various agar mediums containing dextrose the

28. Zinsser, H., and Bayne-Jones, S.: Textbook of Bacteriology, ed. 8, New York, D. Appleton-Century Company, Inc., 1939, pp. 746-751.

29. Gay, F. P.: Agents of Disease and Host Resistance, Springfield, Ill., Charles C. Thomas, Publisher, 1935, pp. 1109-1151.

fungus produces a moist, cream-colored growth, which often becomes yellow or darkened with age. On maltose agar the colony assumes a deep brown color.

PATHOLOGY

C. hominis is pathogenic for mice and rats, while rabbits, guinea pigs and dogs have been found only slightly susceptible. Intraperitoneal injections into rats and mice result in lesions involving the meninges, brain, lungs, liver and spleen, with the peritoneum but slightly affected.

In human beings there is a predilection for the central nervous system and the lungs; visceral involvement is much less common. The skin and skeletal systems have been rarely affected, the site of the lesions differing in this respect from that in the diseases due to the two related organisms. According to Ball,[30] 4 instances have occurred in which the infection was localized. In the case of Brewer and Wood [31] the infection affected the muscles of the vertebral column, in that of McGehee and Michelson,[32] it was localized to a pelvic and inguinal abscess, in that of Berghausen [33] to the tongue and in that of Jones [34] to the nasopharynx. Kessel and Holtzwart [35] reported an interesting case of torula infection of the knee. Rappaport and Kaplan,[36] Weidman [37] and Mook and Moore [38] reported torulosis of the skin. Levin [11] found 8 cases of generalized torula infection, and Longmire and Goodwin [12] added another.

With the exception of the cerebrospinal system, torula infection results in a defensive cellular reaction, similar to that observed in the tissues of infectious granulomas generally. The lesions, consisting of small nodules or tubercles, varying from 0.5 to 8 mm., have as one of their most striking characteristics a large content of mucinous material, evidently a product of their parasitic growth. As the tissue is invaded

30. Ball, H. A.: Human Torula Infections: A Review, California & West. Med. **32**:338 (May) 1930.

31. Brewer, G. E., and Wood, F. C.: Blastomycosis of the Spine; Double Lesion; Two Operations; Recovery, Ann. Surg. **48**:889, 1908.

32. McGehee, J. L., and Michelson, I. D.: Torula Infection in Man, Surg., Gynec. & Obst. **52**:803 (June) 1926.

33. Berghausen, O.: Torula Infection in Man, Ann. Int. Med. **1**:235 (Oct.) 1927.

34. Jones, E. L.: Torula Infection of the Nasopharynx, South. M. J. **20**:120 (Feb.) 1927.

35. Kessel, J. F., and Holtzwart, F.: Experimental Studies with Torula from a Knee Infection in Man, Am. J. Trop. Med. **15**:467 (July) 1935.

36. Rappaport, B. Z., and Kaplan, B.: Generalized Torula Mycosis, Arch. Path. **1**:720 (May) 1926.

37. Weidman, F. D.: Cutaneous Torulosis, South. M. J. **26**:851 (Oct.) 1933.

38. Mook, H. W., and Moore, M.: Cutaneous Torulosis, Arch. Dermat. & Syph. **33**:951 (June) 1936.

by the fungus, it becomes dissolved and replaced by the parasites and their covering, with little evidence of inflammatory reaction. Particularly in tissues other than the central nervous system, the structure of the nodules may be like that of miliary tubercles, composed of giant, epithelioid and lymphoid cells with few polymorphonuclear leukocytes. The torula organisms may or may not be visible in the lesions. Each organism is seen to be surrounded by a circular zone of homogeneous, clear and slightly basic-staining mucin. The presence of caseation has been considered the result of lytic action of the organisms or their products. In the older lesions areas of hyalinization may be discovered.

The reaction of the tissues in the cerebrospinal type of disease is reportedly less marked. Freeman [17] classified the gross pathologic process under three types, the first of which he described as the chronic meningeal form, with diffuse granulomatous meningitis resulting in meningeal thickening and cortical adhesions. Microscopically, the picture resembled a lytic process of the brain substance produced by the invading parasites without an adequate inflammatory-reparative reaction. The second, or perivascular, form, with small granulomas or cysts in the cortex, extended from the surface of the brain along the course of the vessels into the cerebral parenchyma. He found the perivascular type associated frequently with the meningeal. In the third, or embolic, form the lesions were deeply placed, lying chiefly in the gray matter of the basal ganglions, although occasionally in the white matter of both the cerebellum and the cerebrum. Stoddard and Cutler [7] and Freeman [17] have also noted degenerative changes in the ganglion cells with increased neuroglia formation and degeneration of myelin sheaths.

Longmire and Goodwin [12] criticized such a classification. After studying the types of lesions reported, they found cases in which all degrees of cellular reactions in the brain and meninges were shown. They therefore expressed the opinion that with the gradual shading of one type of reaction into the next it was difficult to make any sharp separation of the cases into three distinct classes. It was their experience that the degree of resistance offered to the growth of the fungus from tissue to tissue, even in different parts of a single organ, varied as much as did the general resistance in different persons. Crone, DeGroat and Wahlin [20] found a similar variability in different patients.

COMMENT

As can be appreciated from the preceding case reports, the course of torula infection in case 4 was strikingly different from that in the others, in which death occurred within a few months, the usually recorded duration of the disease. At the time of writing the duration of illness in case 4 has been more than two and half years, which, though

longer than usually recorded, is not longer than has occasionally been noted. In view of the improvement, it will be interesting to discover whether or not this case is another instance of a remission or the beginning of recovery. Inasmuch as no patients with cerebrospinal torulosis have reportedly survived, it seems that eventual recovery is unlikely. Such a noticeable variation in the duration of the illness must be related in some way to a difference in the general resistance of the host, as well as to a variation in the virulence of the fungus.

Although various methods of treatment have been attempted, none has been of any significant benefit. Although the fourth case represents one of the first opportunities for the use of sulfapyridine in treatment of this infection, improvement in this case was evident prior to its trial. Sulfapyridine was also used three days prior to the death of the patient in case 6, without any beneficial effect. Interestingly, in the fourth case both the culture of the spinal fluid and the culture obtained from the involved area of the lung during the course of illness in India failed to reveal the presence of the fungus. This may have been due to the fact that the cultures were not given sufficient time for the organism to make its appearance on ordinary mediums. The importance of further examinations under such circumstances becomes evident and is further emphasized by the fact that in the first and third cases numerous cultures and examinations were made before the organism was discovered.

With the exception of the fourth case, in which the condition was first thought due to syphilis because of the positive Wassermann reactions, the presumptive diagnosis was tuberculous meningitis. Although the proper diagnosis was established in all cases prior to death or autopsy, it was made possible only by the laboratory data.

Because of the pathologic condition, case 6 was felt to represent another example of generalized torula infection.

SUMMARY AND CONCLUSIONS

Torulosis, or cryptococcosis, is a chronic fungous infection which, because of its protean manifestations, simulates tuberculous meningitis, tumor or abscess of the brain or encephalitis when involving the central nervous system, for which it has a special predilection.

Its diagnosis, often difficult, as evidenced by the presented cases, can only be ascertained by the growth of the fungus from the spinal fluid and its differentiation by laboratory methods from other infectious granulomas, such as blastomycosis and coccidioidal granuloma.

That the condition is uncommonly experienced is shown by the fact that when the presented cases are included with those recently reported the total number collected at the present time is only 79.

In spite of various efforts at treatment, none has proved effective, and in all proved cases of involvement of the central nervous system the disease has always progressed to a fatal termination. Our fourth case is of interest because there has been continued improvement in spite of a duration of the illness of more than two and a half years. Our sixth case represents, we believe, a generalized type of the infection.

The noticeable variation in the duration of torula meningitis must be related in some way to a difference in the general resistance of the host, as well as to a variation in the virulence or type of the fungus.

FUSOSPIROCHETOSIS

RECOVERY OF THE CAUSATIVE ORGANISMS FROM THE BLOOD, WITH REPORT OF TWO CASES

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Although a large number of spirochetal diseases have been described, in only a few have the causative organisms been cultured from the blood. Larson and Barron [1] observed a patient with Vincent's stomatitis and osteomyelitis who died after seven weeks of a severe febrile illness. Two days before death a sample of the patient's blood was cultured on ascitic agar in a Novy anaerobic jar at 37 C. After a few days fusiform bacilli appeared in the culture. Attempts were made to subculture these organisms on plain agar, ascitic broth, plain broth, ascitic agar and Löffler's blood serum. No aerobic growth was observed. Growth occurred in all of the anaerobic cultures except the one containing plain agar only. Optimum growth occurred on ascitic agar. When horse blood agar was used some of the organisms exhibited a few spirals. Larson and Barron expressed the belief that the spiral organisms were modified forms of the fusiform bacilli, but they did not describe in detail the characteristics of the spiral structures. Rabbits, guinea pigs, mice and rats were inoculated. Intravenous, subcutaneous, intraperitoneal, intratesticular and intraocular injections were made, with negative results.

Reiter [2] observed a patient with cystitis, arthritis and conjunctivitis. Blood cultures in blood–ascitic beef broth yielded spirochetes, which possessed from seven to ten spirals and exhibited boring movements. No fusiform bacilli were observed. The spirochetes stained intensely with Löffler's methylene blue (methylthionine chloride) and were pathogenic for mice.

Videla and Rey [3] studied a patient who had Vincent's angina, enlargement of the cervical lymph nodes and phlebitis of some of the veins

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1. Larson, W. P., and Barron, M.: Report of a Case in Which the Fusiform Bacillus Was Isolated from the Blood, J. Infect. Dis. **13**:429-437 (Nov.) 1913.

2. Reiter, H.: Ueber eine bisher unerkannte Spirochäteninfektion (Spirochaetosis arthritica), Deutsche med. Wchnschr. **42**:1535-1536 (Dec. 14) 1916.

3. Videla, C. A., and Rey, J. C.: Angina de Vincent. Septicemia venosa subaguda, Rev. Asoc. méd. argent. **47**:1898 (Jan.) 1933.

of the neck. Fusiform bacilli and spirochetes were observed in smears of the pharyngeal exudate. Cultures of the blood yielded no growth. Nevertheless, on the basis of the clinical picture, the condition was diagnosed as "subacute venous septicemia."

Palmer [4] recently observed a patient who had a prolonged illness, with vague pains in the muscles and joints, relapsing fever, a rash resembling that of German measles, arthritis and pericarditis No organisms were cultured from the blood, but spirochetes, measuring about 15 microns in length and possessing three to five spirals, were demonstrated many times in dark field preparations. Blood from the patient was inoculated intraperitoneally into a rat. Spirochetes in the rat's blood were discovered ten days after inoculation. The type of spirochete was not established.

In May 1938 there was admitted to the Vanderbilt University Hospital a patient with arthritis from whose blood fusiform bacilli and spirochetes were subsequently cultured eleven times. After this experience it became the custom in the clinical bacteriologic laboratory to culture all specimens of blood both aerobically and anaerobically and to examine specimens of the blood cultures under dark field illumination. In July 1938 fusiform bacilli and spirochetes were recovered from the blood of a second patient with multiple arthritis and an acute febrile illness.

Fusospirochetal infections are common, and metastatic lesions are not infrequent. The occurrence of the latter indicates that invasion of the blood stream sometimes takes place. Nevertheless, actual recovery of the organisms from the blood has been rare. In fact, the only instance of proved fusospirochetemia which we have found in a survey of the literature is that reported by Larson and Barron.[1] Consequently, a detailed account of the 2 cases observed at Vanderbilt University is presented.

REPORT OF CASES

CASE 1.—E. D., a bus driver aged 28, was admitted to the hospital May 18, 1938 complaining of arthritis. He had considered himself well until July 1936, although for several months preceding this time a creamy urethral discharge had been present. On July 28, 1936 fever developed, with severe headache and generalized malaise. Within a short time most of the joints of the extremities became swollen, red and tender, and he became delirious. After approximately seven weeks of severe illness a tonsillectomy was performed. Three days later his sensorium became normal; fever disappeared shortly thereafter. The condition of the joints exhibited considerable improvement, but soreness and stiffness were noticed periodically. The left leg had been immobilized in a cast for five

4. Palmer, L.: Spirochetal Blood Stream Infection of Undetermined Type: Report of Case, South. M. J. **31**:530-534 (May) 1938.

weeks during the acute illness. After removal of the cast, the ankle and knee remained stiff.

In January 1938 gonococci were obtained from the urethral discharge. The patient was treated by means of urethral irrigations and by the use of sulfanilamide. However, urethritis persisted, and he was admitted to the hospital for fever therapy.

Physical Examination.—The temperature was 99 F., the pulse rate 88, the respiratory rate 18 and the blood pressure 148 systolic and 94 diastolic. The patient did not appear ill. His nutritional state and muscular development seemed good. No abnormalities of the skin or the mucous membranes were observed. The epitrochlear lymph nodes were slightly enlarged, but the superficial nodes elsewhere were of normal size. The tonsils and teeth had been removed. Examination of the heart and lungs revealed no abnormalities. The liver could not be felt, but the edge of the spleen was palpable 6 cm. below the left costal margin. The splenic surface was firm and smooth but not tender. The left knee was swollen and appreciably limited in motion. The left ankle and the phalangeal joints of the left foot were almost completely ankylosed. A slight increase in the temperature of the skin over the left ankle was noted, but there was no edema.

Laboratory Data.—The urine was normal. The leukocyte count was 4,900 per cubic millimeter, the hemoglobin content 15 Gm. per hundred cubic centimeters and the Wassermann reaction of the blood negative. Many gram-negative intracellular diplococci were found in the urethral discharge. The complement fixation test for gonococcic infection was positive. Roentgenograms revealed narrowing of the joint apexes of the left knee and left ankle and marked roughening of the articular surfaces. The patient's serum in a dilution of 1:1,280 agglutinated Bacillus abortus and Bacillus melitensis. The opsonocytophagic test for brucellosis revealed marked phagocytosis by most of the cells. The patient exhibited a strong intradermal reaction to 0.1 cc. of brucellergen.

Course.—The first hyperthermal treatment was given May 20, without noticeable change in the patient's condition. On May 23 a second hyperthermal treatment was administered, his temperature being maintained betwen 106 and 107 F. for five hours. Two days after this treatment he experienced nausea, epigastric distress, a shaking chill and elevation of temperature to 104 F. (fig. 1). On May 27 he was slightly jaundiced (icterus index 21). There appeared in the skin of the legs and trunk many hot, round, erythematous lesions, 5 to 20 mm. in diameter. They were not raised or tender. Some of the lesions had a purplish tinge (fig. 2). Two blood cultures were made on this day. (See "Bacteriologic Studies.") One week later both cultures were found to contain fusiform bacilli and spirochetes.

On May 28 the patient complained of pain low in the left axilla, and the following day a pleural friction rub was heard over this area. It disappeared after forty-eight hours. The jaundice subsided in a few days and did not recur.

A third hyperthermal treatment was given June 6, and a fourth was begun two days later but was discontinued because of the development of marked shortness of breath and abdominal cramps.

On June 14 intravenous injections of 0.6 Gm. of neoarsphenamine were instituted at intervals of about seven days. Febrile reactions followed several of these treatments. On July 4 the reaction to neoarsphenamine was so severe that it was

decided to employ silver arsphenamine in the future. The patient received weekly injections of 0.3 Gm. of silver arsphenamine and biweekly injections of 2 cc. of a 1.5 per cent solution of bismuth sodium tartrate for the next three months. After the first injection of bismuth a sharp and more prolonged febrile reaction developed, but none occurred subsequently.

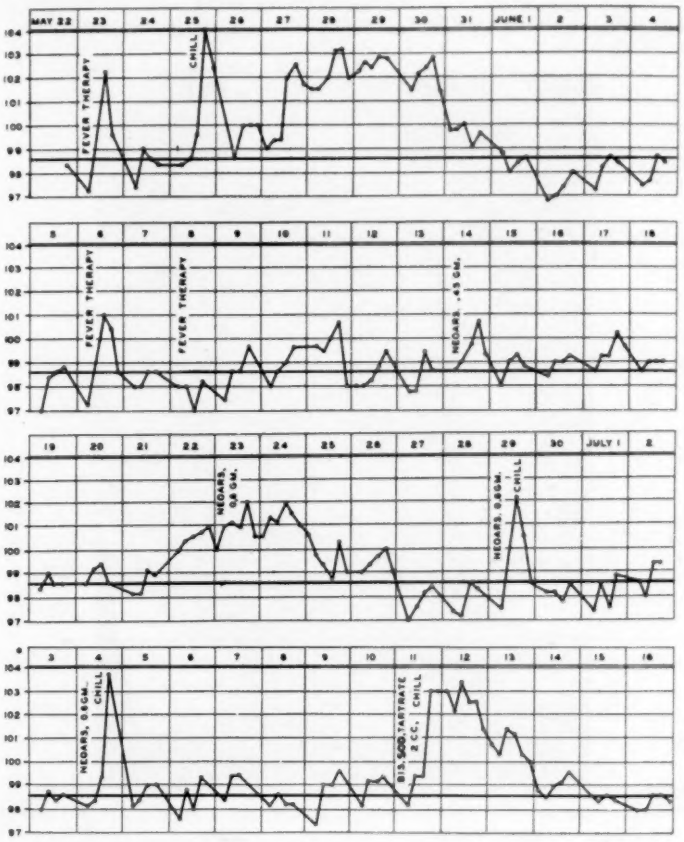

Fig. 1 (case 1).—The temperature chart. Note reactions to treatment.

The patient remained in the hospital two months. He complained of slight pain in the joints from time to time. They occasionally exhibited evidence of mild, acute inflammation. The splenic enlargement persisted, and the erythematous lesions were still present at the time of the patient's discharge from the hospital.

Throughout his stay in the hospital cultures of the blood were made periodically. Spirochetes and fusiform bacilli were demonstrated in eight of a total of thirteen

such cultures. Several dark field examinations of the patient's blood were made, but no organisms were revealed. Furthermore, neither fusiform bacilli nor spirochetes were found in the urine, stools or urethral discharge by either dark field examination or culture.

A year and a half has elapsed since the first admission of the patient to the hospital. His course has been followed closely in the outpatient department, and he has been readmitted to the hospital twice for study. During this elapsed period he has been out of bed most of the time and in general has felt well.

Fig. 2 (case 1).—Erythematous eruption with hemorrhages in some areas.

The cutaneous rash disappeared in September 1938 and did not recur. He has had two bouts of fever. In January 1939 his temperature rose daily to about 102 F. for a few days and in June to about 104 F. In both attacks he experienced persistent aching pain in the joints. During the year and a half the results of physical examination have not changed. The abnormalities of the joints have remained stationary, and splenic enlargement has persisted.

After the patient was discharged, blood cultures were made monthly for ten months. Three of these yielded fusospirochetes. The last positive culture was

obtained Oct. 11, 1938, three months after the termination of his first stay in the hospital. Seven subsequent cultures were negative. The characteristics of the organisms are recorded below.

Special Bacteriologic Studies.—On May 27, 20 cc. of the patient's blood was drawn into 20 cc. of a 1.5 per cent solution of sodium citrate. Cultures were made as follows: Portions measuring 0.5, 1.0 and 1.5 cc. were mixed with 3 per cent beef infusion agar (p_H 7.6) and poured into Petri dishes. A tube of beef infusion broth containing sterile ascitic fluid was also inoculated. The remaining blood was placed in a 300 cc. Florence flask containing dextrose-infusion broth (p_H 7.7) to which had been added 20 cc. of sterile ascitic fluid. One of the blood agar plates and the two broth cultures were covered with a layer of sterile melted petrolatum.

Fig. 3 (case 1).—Drawing (× 2,250) of various organisms observed in a dark field preparation of a blood culture. Note the extreme pleomorphism.

All of the cultures were incubated at 37 C. After two days the broth in the flask appeared cloudy, and slight hemolysis was present. On microscopic examination actively motile, slightly gram-positive, fusiform rods were observed. No organisms were found in the other cultures. The flask was placed in a jar of carbon dioxide under 75 mm. pressure. At the end of three days increased turbidity and hemolysis was observed. Smears stained by the Gram method revealed no organisms, but the examination of wet preparations by bright and by dark field illumination revealed the presence of many spirochetes. These organisms were subcultured nine times. The culture was then discarded.

As has been stated, twenty-three cultures of the blood were made, and eleven yielded fusiform bacilli and spirochetes. Many of the strains of these organisms were subcultured repeatedly.

Morphologic Characteristics: One of the most outstanding characteristics of the organisms was their pleomorphic nature (figs. 3, 4 and 5). Measurements of

several hundred spirochetes gave the following results: length, 6 to 45 microns, with an average of 15 microns; width, 0.4 to 0.8 micron, with an average of 0.6 micron; spiral amplitude, 2 to 6 microns, with an average of 3 microns, and spiral depth, 1.2 to 2.5 microns, with an average of 1.8 microns. The number of spirals varied from two to thirty-five, with an average of five. In some organisms the spirals were close together, but in the majority they were widely spaced. Some of the spirals were irregular. The ends of the organisms were sharply pointed. Some of the larger organisms had a double contour. No flagella, crista or chambered structure was observed. The fusiform bacilli varied somewhat in size but the average length was about 10 microns and the average width 0.8 micron. The ends were tapered and pointed.

The commonest type of motion was of a corkscrew-like, boring variety, although serpentine motion was observed. At times the larger spirochetes moved like earthworms and rarely exhibited rotary movements. There was great variation in the speed of motion, the smaller forms moving more rapidly. The fusiform bacilli darted back and forth quickly in a shuttle-like fashion.

Fig. 4 (case 1).—Spirochetes (× 2,000), stained by Fontana's method, in a blood culture.

Multiplication was by transverse division.

Staining Reactions: The spirochetes stained rather well with Fontana's stain (fig. 3) and moderately well with Wright's stain. The effectiveness of Wright's stain was increased by using slides previously treated with a film of brilliant cresyl blue.

Cultural Characteristics: The organisms grew best at 37 C. in 300 cc. flasks of dextrose–beef infusion broth containing a small amount of blood and ascitic fluid. The cultures were covered with melted petrolatum and the flasks placed in a jar containing carbon dioxide under 75 mm. pressure. No growth occurred at room temperature. Although anaerobic conditions were obligatory for initiating growth in blood cultures, subcultures under aerobic conditions yielded growth. Blood and ascitic fluid were necessary elements of the mediums in most instances, although on a few occasions the organisms were cultured in plain beef infusion broth.

The fusiform bacillus was usually the first form to appear in the cultures and was observed in cultures three to seven days old. A few days later short spirochetes appeared. During the next two weeks the spirochetal forms appeared to increase in length, breadth and number but to decrease in motility. The more numerous the spirochetes, the smaller the individual organism.

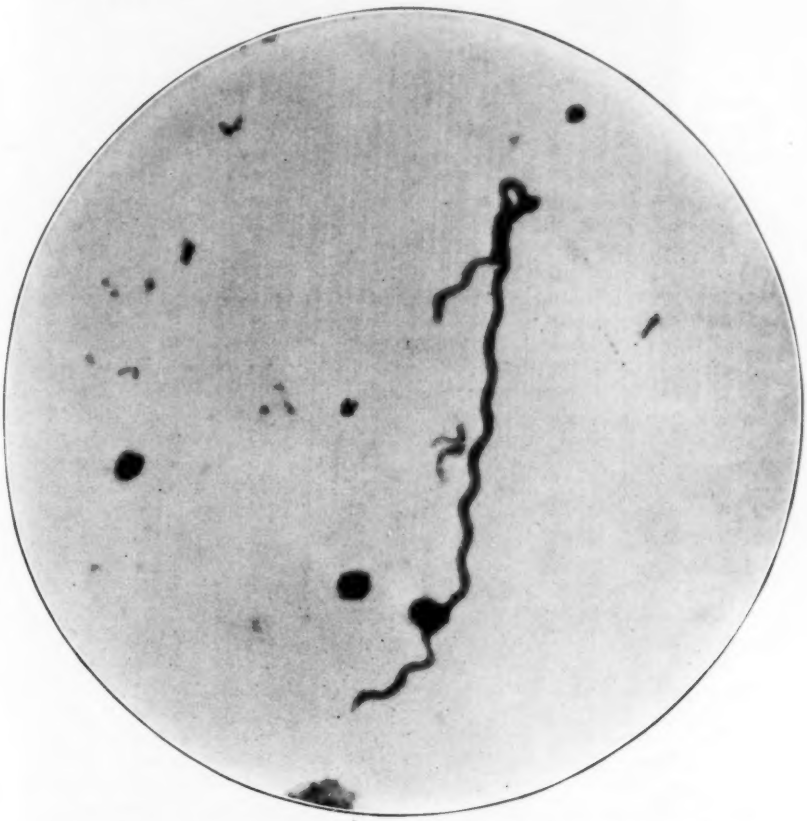

Fig. 5 (case 1).—Spirochetes (× 3,000), stained by Fontana's method, in a blood culture.

After about four weeks most of the cultures acquired a putrid odor and exhibited gas formation. Cultures at this stage contained, in addition to fusiform bacilli and spirochetes, many short rods which were nonmotile, stained irregularly and, except for greater thickness, resembled diphtheroid bacilli. At this stage in two cultures many of the spirochetes gave the appearance of branching (fig. 6). Subcultures yielded only the diphtheroid form, which grew well aerobically on blood

agar slants. The colonies were grayish white and resembled those of Staphylococcus albus. The diphtheroid forms fermented dextrose rapidly with the production of gas, but fermentation and gas formation took place slowly with maltose, mannite, xylose, sucrose and lactose. These organisms may represent the type III fusiform bacillus described by Smith.[5]

Fig. 6 (case 1).—Branching forms of spirochetes (× 2,000), stained by Wright's method, in a blood culture.

Special Biochemical Reactions: Under the influence of tryptic digestion the spirochetes remained actively motile and unchanged for more than two days. In the presence of a 10 per cent solution of bile salts most of them were dissolved within two hours. With a 10 per cent solution of saponin they became immobile in one

5. Smith, D. T.: Oral Spirochetes and Related Organisms in Fuso-Spirochetal Disease, Baltimore, Williams & Wilkins Company, 1932.

hour and were partially dissolved in two hours. With distilled water they were motile at the end of two days and showed no plasmolysis.

Animal Inoculation: A large number of animals were inoculated in various sites with cultures and with the patient's blood. A Macacus rhesus monkey, mice, rats, guinea pigs and rabbits were employed. Some of the blood was collected in a solution of sodium citrate, and some was injected without an anticoagulant. The animals were observed for periods of five days to three months, and dark field examinations of the blood were made daily for the first two weeks following inoculation and several times a week thereafter. In many instances dark field examinations were made of material from the site of injection. The blood and other body fluids of the animals were cultured frequently. However, spirochetes or fusiform bacilli were rarely recovered. Many animals were killed and subjected to postmortem examination. No macroscopic lesions were observed, and microscopic examination of the viscera revealed no significant abnormalities. These negative observations may be summarized as follows: Samples of original blood cultures containing numerous motile spirochetes were inoculated as follows: (1) intraperitoneally into 5 rats, 4 guinea pigs, 2 mice and 1 Macacus rhesus monkey; (2) intravenously into 2 rabbits; (3) intratesticularly into 2 rabbits, and (4) subcutaneously into 2 rats, 2 guinea pigs and 2 rabbits. Although this experiment indicated, in the main, that the organisms possessed but little virulence for the species of animals used, certain other animal experiments are of possible significance and are worthy of record.

On July 15 a dark field examination was made of blood from a rabbit. No organisms were observed. A blood culture was also made, but it yielded no growth. Then the animal was inoculated intravenously with 10 cc. of patient E. D.'s blood in a solution of sodium citrate. Two days later a few spirochetes were observed in a dark field preparation of the rabbit's blood. However, the organisms could not be grown in culture, and, in spite of frequent dark field examination during the next two months, their presence in the blood could not be demonstrated again.

On July 29 a rat was inoculated intraperitoneally with 5 cc. of fresh whole blood from patient E. D. The rat died August 4. Dark field examinations of the heart blood and the peritoneal fluid revealed no spirochetes. However, in the peritoneal fluid many coarse granular structures were observed. Petrolatum was placed around the edges of the cover glass, and the slide was preserved at room temperature. The following morning a few motile spirochetes were observed. A week later postmortem cultures of the peritoneal fluid of this rat contained numerous motile spirochetes. Within another week the culture contained organisms of the same size and appearance as those in the cultures made directly with the patient's blood. The organisms from peritoneal fluid were subcultured successfully three times. A postmortem culture of the heart blood of the rat remained sterile.

On August 16 samples of blood from 4 rats were examined under dark field illumination and were cultured. No spirochetes were observed, and the cultures yielded no growth. The rats were inoculated intraperitoneally with a fourth subculture of the patient's blood. Dark field examinations of blood from these rats were made daily and were negative for spirochetes. Several cultures of the heart blood of 3 rats remained sterile; a culture of blood from the heart of rat 4, made August 19, was found to contain a few slender spirochetes two weeks later. A second culture, made August 24, also yielded spirochetes. The animal died September 2. No organisms were revealed by dark field examinations of the heart blood and the peritoneal fluid. Rat 1 died two weeks after inoculation. A dark field examination of the blood showed no organisms. In the peritoneal fluid there

were many motile spirochetes and motile rods. The spirochetes appeared morphologically similar to those in cultures of the patient's blood. Cultures were made of the rat peritoneal fluid, brain and heart blood. Motile spirochetes and rods were found after one week and were subcultured successfully, without difficulty. Rats 2 and 3 remained normal. They were killed four weeks after inoculation. Postmortem cultures and dark field examinations gave negative results.

On August 22 a rat which had been shown by a culture and a dark field examination of the blood not to have preexisting spirochetosis was inoculated intraperitoneally with 5 cc. of the patient's whole blood. No anticoagulant was employed. Frequent cultures and dark field examinations of the animal's blood revealed no organisms. Finally, a culture, made September 15, yielded spirochetes. No subcultures were made. The animal survived. Subsequent dark field examinations of the blood revealed no organisms.

Since it had been established that the patient had a gonococcic infection and undulant fever, it seemed important to determine whether experimental infection with the spirochetes obtained from his blood could be established more regularly in animals in the presence of another infectious agent. Three rats which had been shown previously to be free of spirochetes, by culture and dark field examination of the blood, were used. The animals were inoculated intraperitoneally with a broth suspension of gonococci to which had been added 0.5 cc. of culture of the spirochetes (obtained from the patient's blood). The animals were killed on September 22. Dark field examinations of the heart blood and peritoneal fluid revealed no organisms. Cultures of the blood and fluid from 2 of the rats remained sterile. On September 29 a culture of the heart blood of the third rat was found to contain spirochetes. These were transferred successfully through several generations.

Case 2.—E. M., a white man aged 24, was admitted to the hospital June 27, 1938 complaining of pain and swelling about the left hip. He stated that he had felt well until four days previously, when chilliness developed, with fever, prostration, anorexia and nausea. Within a few hours severe pain in his head, arms, back and legs occurred. Three days later the left hip became swollen, red and painful. The following day these symptoms were more marked, and he came to the hospital.

At the age of 10 he fell off a pony and landed on the left hip. The injury did not seem severe at the time, but one year later it was noted that he favored this leg in walking.

One month before his admission to the hospital a rat bit him on one finger. The injury appeared trivial, and it healed within a few days, without apparent scar formation.

Five days before the onset of the febrile illness he had been working in a swamp and was bitten by many mosquitoes.

Physical Examination.—The temperature was 102.4 F., the pulse rate 88 and the respiratory rate 22. He was restless and complained of a great deal of pain about the left hip, but he did not appear to be seriously ill. He was not undernourished. The skin was normal. The cervical, axillary and inguinal nodes were slightly enlarged. The heart and lungs were normal. The spleen and liver were not felt. There were no abnormalities in the joints, except about the left hip. There were some atrophy of the muscles of the left hip and slight shortening of the left leg. The skin over the hip was red, hot and tender, and movements in the hip joint were painful.

Laboratory Data.—The urine was normal. The hemoglobin content was 13.2 Gm. per hundred cubic centimeters of blood, the red cell count 5,090,000 per cubic millimeter and the white cell count 11,300, with a normal differential count. The Kahn reaction of the blood was negative. Examination of a stool did not reveal blood, pus or parasites. Repeated examinations of prostatic secretion showed no gonococci. A thick smear of the blood was negative for the causative organisms of malaria. The patient's serum did not agglutinate any of the following organisms: Bacillus typhosus, Bacillus paratyphosus A and B, B. abortus and B. melitensis. The opsonocytophagic test for brucellosis showed no phagocytosis. The cutaneous test with brucellergen gave no reaction. The complement fixation test for gonococcic infection was negative. Two electrocardiograms were normal. A roentgenogram of the left hip exhibited changes interpreted as Legge's disease (osteochondritis deformans juvenilis).

Course.—In spite of frequent doses of acetylsalicylic acid and codeine sulfate, the pain in the left hip was so severe that the patient was given morphine sulfate on several occasions. Two unsuccessful attempts were made to aspirate fluid from the joint. For two weeks his temperature fluctuated between 101 and 103 F. Two days after the patient's admission to the hospital moderate swelling, redness, tenderness and increased heat developed about the proximal interphalangeal joint of the index finger on the left hand. The following day inflammation here had largely subsided, but the pain in the hip had increased. Two days later signs of acute inflammation of the left wrist developed and persisted for about twenty-four hours. Subsequently transitory pains occurred in the right ankle and right shoulder.

The patient's temperature gradually fell during the third and fourth weeks of his stay in the hospital. On July 25, approximately one month after his admission and after he had become free of fever, he received 0.6 Gm. of neoarsphenamine. The treatment was borne well, and he was given two subsequent injections before discharge on August 3. Two blood cultures were made between July 25 and August 3. Both remained sterile after long periods of incubation.

Bacteriologic Studies.—Dark field examinations of the patient's blood and urine were negative for spirochetes. Cultures of the urine yielded no growth. Cultures of the blood made June 28 and July 1 remained sterile. A third blood culture, made July 2, yielded spirochetes and fusiform bacilli after eleven days of incubation. The culture methods employed were the same as those described in case 1. The organisms observed in dark field preparation and in stained specimens appeared identical with those in case 1. The first subculture yielded good growth. Subsequent subcultures remained sterile. A sample of the original culture was inoculated intraperitoneally into a rat and a guinea pig. Dark field examination and cultures of the blood of these animals did not reveal spirochetes or fusiform bacilli. A sample of the patient's blood was collected in a solution of sodium citrate and inoculated intraperitoneally into a rat and a guinea pig and intravenously into a rabbit. No spirochetes or fusiform bacilli were found subsequently, in spite of frequent dark field examinations of specimens of blood from these animals.

COMMENT

The courses of the illness experienced by the 2 patients were similar in many respects. The initial symptoms of illness in both instances resembled those of rat bite fever, relapsing fever and Weil's disease. Fever suddenly developed, associated with chilliness, prostration, head-

ache and aching in muscles and joints and, subsequently, with migratory arthritis. The arthritis was accompanied by objective manifestations. The first patient, E. D., suffered from an intermittent type of arthritis for two years, whereas the second patient, E. M., was free of arthritic symptoms after one month. Over a period of two years E. D. experienced occasional bouts of fever, which varied in duration from a few days to several weeks. E. M. was observed early in the course of his infection and was febrile for five weeks. The subsequent course, after treatment, is unknown.

On physical examination both patients presented evidence of arthritis. In one, E. M., the manifestations were acute, and in the other, chronic, with acute exacerbations. There was slight enlargement of some of the superficial lymph nodes in both patients and of the spleen in one, E. D. In E. D., a hemorrhagic rash, slight jaundice and acute pleuritis also developed. In neither patient was the infection associated with anemia. There was never more than slight leukocytosis. Wassermann and Kahn reactions were negative. Spirochetes could not be demonstrated by direct examination of the blood, although they were cultured from the blood of the first patient eleven times and from that of the second patient once. They were not found in the urine of either patient.

On the basis of the criteria for the identification of spirochetes presented by Noguchi [6] and by Hindle,[7] it appears that the organisms which we recovered belong to the genus Spirochaeta and are the type encountered in Vincent's angina.

The main characteristics of the spirochetes which we recovered may be summarized. The average measurements, expressed in microns, were: length 15, width 0.6, spiral amplitude 3 and spiral depth 1.8. The number of spirals varied from two to thirty-five. The motion was usually corkscrew-like, but serpentine, earthworm-like and rotary movements were also observed. Fusiform bacilli of varying sizes were usually found with the spirochetes. The latter organisms readily took either Fontana's or Wright's stain. They grew well in dextrose–infusion broth containing ascitic fluid if the surface was covered with petrolatum and if they were incubated at 37 C. in a jar containing carbon dioxide. They usually grew out in a week and continued growing in the same culture for more than a month, producing a foul odor. Subcultures were made as many as nine times. The organisms were resistant to

6. Noguchi, H.: The Spirochetes, in Jordan, E. O., and Falk, I. S.: The Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, pp. 452-597.

7. Hindle, E.: The Spirochetes, in Arkwright, J. A.; Bedson, S. P., and others: A System of Bacteriology in Relation to Medicine, London, His Majesty's Stationery Office, 1931, vol. 8, pp. 101-138.

tryptic digestion but were almost completely disintegrated and dissolved in the presence of a 10 per cent solution of bile salts or of saponin. They were mildly pathogenic for rats, 1 rat dying one week and 1 rat two weeks after intraperitoneal inoculation. The organisms were found in either the heart blood or the peritoneal fluid of 5 rats, sometimes by direct dark field examination and at other times by culture. They were observed about two weeks after the animals had been inoculated intraperitoneally. They were recovered either when the patient's blood or a culture of the blood was used as the inoculum. Successful subcultures were made repeatedly.

Both patients apparently were benefited by treatment with arsphenamine. Clinical improvement followed, and fusiform bacilli and spirochetes seemingly disappeared from the blood. The first patient seemed to have the equivalent of a Herxheimer reaction after the administration of neoarsphenamine. Fever therapy appeared to exert a similar effect.

The source of infection in patient E. D. was possibly the tonsils, since they had been the source of symptoms for years. It is known that tonsils often harbor fusiform bacilli and spirochetes. The rat bite is considered the source of infection in the second patient. Smith [5] has found fusospirochetes in the mouths of rats.

It is difficult to evaluate the role of brucellosis and gonococcic infection in the first patient. It is possible that these infections may have operated as factors favoring fusospirochetal infection.

SUMMARY

The recovery of fusiform bacilli and spirochetes, of the type found in Vincent's angina, in cultures of the blood of 2 patients is recorded. Fusospirochetes were recovered eleven times from 1 patient and once from the other. Successful subcultures of the organism were made repeatedly. The organisms were slightly pathogenic for rats.

In the 2 patients fusospirochetemia was associated with an illness characterized by the sudden development of fever, prostration, headache, myalgia and migratory arthritis. In 1 patient splenomegaly developed, with jaundice, a hemorrhagic eruption and acute pleuritis. The source of infection is considered to be the tonsils in 1 instance and the bite of a rat in the other.

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CAUSE OF THE SO-CALLED SIDE ACHE THAT OCCURS IN NORMAL PERSONS

PERSONAL OBSERVATIONS

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The "side ache," or "stitch in the side," that occurs with exercise in normal persons is well known to layman and to physician alike. It was mentioned by Pliny the Elder and by Shakespeare. In spite of its frequent occurrence, it has received little attention in the medical literature. Explanations regarding its mechanism have been largely speculative. I have been able to find only four papers in which actual data concerning its nature have been recorded. Benjamin,[1] in 1923, stated that this pain occurred only in "constitutionally inferior children." He claimed that because of faulty vasomotor regulation, exercise resulted in congestion and swelling of the liver and the spleen. The pain was due to visceral distention and to pulling on the suspensory ligaments. He stated that relief was obtained by deep breathing, by tightening of a belt or by local external pressure. He detected enlargement of the liver and the spleen by percussion. In 1927 Herxheimer [2] carefully studied 42 children and young persons between the ages of 10 and 20 years. He concluded that pain was due to a pulling on the suspensory ligaments of the viscera caused by the bouncing or shaking which accompanies certain forms of exertion. He stated the belief that congestion did not play a role and found no evidence of visceral distention by roentgen or physical examination. According to his data, only walking, running or similar rhythmic bouncing exercise caused this pain. There was no relation to the amount of exertion. Bending over, local pressure or an abdominal binder gave relief. Nassau,[3] in 1935, found that "perverted respiration" was present in patients who had this pain. By this he meant that during inspiration the abdomen relaxes so that there is no increase in intra-abdominal pressure, such as he said normally occurs. Thus, there results a stagnation

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1. Benjamin, K.: Zur Pathogenese der Wachstumsblässe, Jahrb. f. Kinderh. **102**:203, 1923.

2. Herxheimer, H.: Ueber das "Seitenstechen," Deutsche med. Wchnschr. **53**: 1130, 1927.

3. Nassau, E.: Ueber das sogenannte "Seitenstechen" der Kinder, Klin. Wchnschr. **14**:1252, 1935.

of blood in the abdomen with consequent congestion and distention of the viscera. His patients all were of the ptotic body type. Improved respiration resulted in disappearance of the pain. Kugelmass,[4] in 1937, confirmed these findings. Both the last two authors obtained information in the main by asking children to recall their symptoms. Only Herxheimer presented data regarding actual observations on the pain.

A number of other causes have been suggested in the literature. Painful contraction of the spleen was blamed by Bancroft,[5] Mosse[6] and Rautmann.[7] Painful distention of the spleen was suggested by Mosler[8] and R. Schmidt.[9] F. A. Schmidt[10] mentioned pulling on the visceral suspensory ligaments and on the diaphragm. Finally, Pembrey[11] expressed the opinion that spasm of the intercostal muscles was the cause.

Because of the diverse views concerning this phenomenon, and especially because of the relative lack of accurate firsthand information regarding its characteristics, it seemed desirable to reinvestigate the problem.

MATERIAL

Personal observations were made over a period of several years on different groups of persons subject to this pain. By watching the track team of the University of Chicago High School through their winter track season I noted many cases. A few college track men were seen during the same period. Men out of training were observed in an impromptu professional-school track meet at the downtown campus of Northwestern University and likewise in an interfraternity turkey race among college students in Evanston, Ill. Cases were also seen among students engaging in other sports, such as wrestling and basketball, through the coaching staff at Northwestern University. A number of cases were noted and carefully observed among friends. A few examples were found among patients. Finally, interesting data were obtained from a number of professional coaches.

RESULTS

General Data.—One hundred and fourteen attacks of so-called side ache were personally observed in 55 different persons. Forty-four of

4. Kugelmass, I. N.: The Respiratory Basis of Periodic Subcostal Pain in Children, Am. J. M. Sc. **194**:376, 1937.

5. Bancroft, J.: Die Stellung der Milz im Kreislaufsystem, Ergebn. d. Physiol. **25**:818, 1926.

6. Moses, M.: Milzstiche, Med. Welt **1**:17, 1927.

7. Rautmann, H. L.: Ertrinkungstod und Wiederbelebung, Med. Welt **1**:1047, 1927.

8. Mosler, F.: Krankheiten der Milz, in von Ziemssens, H.: Handbuch der speciellen Pathologie und Therapie, ed. 2, Leipzig, F. C. W. Vogel, 1878, vol. 8, pt. 2, pp. 1-196.

9. Schmidt, R., cited by Herxheimer.[2]

10. Schmidt, F. A.: Unser Körper, Leipzig, Voigtländer, 1929.

11. Pembrey, cited by Kugelmass.[4]

the subjects were males and 11 were females. The ages ranged from 15 to 65 years, but only 3 were over 35 years of age. Twenty-five of the subjects were seen in more than one attack. All subjects were normal and healthy as far as is known. In several instances a similar pain was observed in diseased persons, but data from these persons were not included in the tables. They are mentioned in the section entitled "Comment." Complete information was, unfortunately, not obtained in every case, so that only definite and reliable data are included.

Location of Pain.—The frequency of the various sites of pain can be seen in table 1. The right or left upper quadrant of the abdomen was the usual location. The 3 subjects with precordial pain and pain in the second left costal interspace had just finished a mile (1.6 kilometers) run and were completely exhausted. This may represent a different type of

TABLE 1.—*Location of Pain in Individual Attacks*

Sites of Pain for Entire Series			
Right upper quadrant of abdomen	51	Right nipple	2
Left upper quadrant of abdomen	33	Right median part of abdomen	2
Epigastrium	6	Substernal area	2
Left median part of abdomen	5	Left costal margin	1
Right costal margin	4	Navel	1
Left lower quadrant of abdomen	3	Left second interspace	1
Precordium	2	Right and left upper quadrants of abdomen	1
Location of Pain in Persons with Two or More Attacks			
Pain always on same side	7		
Pain on different sides	18		
Location of Pain in Strenuous Exertion and in Mild Exertion			
Same location	4		
Different locations	8		
Persons who had pain only with one type of exertion	13		
Same location	9		
Different locations	13		

pain from the ordinary side ache. It should be noted that the site of pain was often not constant in the same person on different occasions. This was true even though the type of exertion was the same. It is noteworthy that shoulder pain was never observed, although it was specifically looked for.

Character of Pain.—The character of the pain was variable. It was described as sharp in 37 cases and as dull in 10. In 2 instances, both of substernal pain, it was constricting. In 1 instance each the sensation was said to be that of pressure, of a cramp and of gnawing. The pain usually lasted only a few minutes, although occasionally it lasted ten to twenty minutes. Tenderness was noted in the region of pain in 8 cases, while in 11 there was no tenderness.

Precipitating Factors.—Physical exertion of some kind was always the chief precipitating factor. Simple twisting or bending of the body alone was never observed to cause this pain. The requisite type of

exercise varied from walking to strenuous running, including both sprints and the longer distances, up to 2 miles (3.2 kilometers). Other forms of exertion, such as horseback riding, swimming, boxing, wrestling, skiing, squash and basketball, were also observed to be adequate cause in individual cases. Although not specifically tested, the amount of exercise required to produce pain in a given person under similar circumstances seemed to be relatively constant.

As seen from table 2, mild exercise, such as walking, was effective in producing a side ache usually only when indulged in soon after a meal. In 4 of the 11 women pain was more likely to occur at the time of menstruation. No correlation was found between the severity or type of exertion and the location or character of the pain. As is seen in table 1, in 4 persons who had pain with both mild and strenuous exercise the pain was in the same location, whereas in 8 others it occurred in different locations. On the other hand, in 9 subjects who

TABLE 2.—*Precipitating Factors* *

Strenuous exertion	51	
Strenuous exertion post cibum	3	
Total	—	54
Mild exertion	16	
Mild exertion post cibum	44	
Total	—	60
Effect of Training		
Pain disappeared with training	2	
Pain failed to disappear with training	3	

* Figures represent individual attacks.

had pain on several occasions the pain experienced during the same type of activity was in the same location, whereas in 13 others it was in different locations.

The effect of physical training was also variable. In 2 persons the side ache definitely disappeared with training, and in 3 others it continued to be present despite excellent training. This variability was confirmed by several coaches, who agreed that in some persons the pain was only present when the physical condition was poor or when the person was "warming up." And yet in other cases no matter how excellent the training, the pain persisted. In some persons it is so severe that nausea and vomiting ensue. Although in a few cases the pain may disappear even though the exertion is continued, this is not usually so. Thus there seems to be no definite relationship to the "second wind."

Cold weather was reported to be a factor by one coach. He described an intercollegiate cross country track meet in which 40 out of 60 competitors were forced to stop and be driven back because of the severity of the side ache. The temperature was around 15 F. In another

instance a cross country team "warmed up" outside in severe cold and were all able to complete the race. The opposing team "warmed up" inside the field house, and all but 1 were forced to drop out of the race because of stitch pain.

Respiration.—Deep breathing increased the pain in 25 instances, had no effect in 33 and gave relief in 3. In 53 attacks this feature was not noted.

Factors Giving Relief.—These are recorded in table 3. It should be noted that either bending over, usually toward the affected side, or pressure with the hand over the painful abdominal region, or both, gave relief in 42 instances. The effect of these maneuvers was, unfortunately, not investigated in the remainder of the subjects. In only 4 instances was bending over found to be ineffective. Tightening of a belt was said by one coach to be of value in enabling some athletes to control the pain and to continue their endeavors. In several carefully observed subjects, bending over stopped the pain though exercise was continued. This

TABLE 3.—*Factors Giving Relief* *

Bending over (failed in 4)	28
Pressure	14
Stopping exertion	32
Holding breath	3
Deep breathing	3
Loosening belt	3

* The figures represent individual attacks. It is to be noted that bending and/or pressure relieved 42 attacks. Of these, 21 were from mild exertion and 11 were from strenuous exertion.

observation was repeated several times. Bending over was found to relieve the pain produced by both mild and strenuous exertion.

COMMENT

The outstanding features of the stitch pain are its relation to exertion, its tendency to occur after eating, its variable location even in the same person in the right or the left upper quadrant of the abdomen and the relief obtained from bending or pressure. These observations are in general confirmed in the literature. The relation to respiration is indefinite, although I found that the pain was often relieved by deep breathing. This is at variance with the observations of Nassau [3] and of Kugelmass.[4] Finally, cold weather appears to be a previously unrecognized predisposing factor. A satisfactory explanation of the mechanism of this pain must take all of these factors into account.

From a consideration of the foregoing data it becomes clear that certain of the proposed theories are obviously untenable. Painful contraction of the spleen [12] fails to explain pain on the right side. Spasm

12. Bancroft.[5] Mosse.[6] Rautmann.[7]

of the intercostal muscles[11] should produce pain over the muscles involved. Furthermore, this hypothesis is not supported by any direct evidence. The pain could hardly be due to pulling on the suspensory ligaments of the viscera, as proposed by Herxheimer,[2] for I have repeatedly observed its appearance during such activities as swimming, skiing and wrestling, in which rhythmic bouncing does not occur to any extent. Also, I have observed a relationship between the appearance of the pain and the extent of the exertion. Certain other possibilities which might come to mind, such as spasm of the intestine and spasm of the abdominal muscles, obviously fail to satisfy the criteria.

The last, and perhaps most generally held, theory is that of congestion and distention of abdominal viscera, due to the heart, to abnormal vasomotor reactions[1] or to faulty respiration.[13] First, it appears unlikely that visceral distention from whatever cause can satisfactorily explain the side ache. Since the pain is usually well to the side, the liver and spleen must be the chief organs involved. It seems unlikely that the splenic and hepatic flexures of the colon would be involved without the rest of the intestine; and, except for these points, intestinal pain should be mostly in the midline.[14] Painful distention of the spleen in clinical conditions associated with venous congestion is certainly unusual and could hardly be expected in the absence of a similar situation in the liver. Herxheimer,[2] in careful studies, including roentgen and physical examinations, found no evidence for enlargement of the liver or the spleen. Furthermore, tenderness, which is nearly always present in the pathologically congested liver, is not a prominent feature of the side ache. Finally, exertion should tend to cause splenic contraction.[5] I have observed a man with mild congestive failure and an enlarged liver who had what was comparable to a stitch pain on exertion, but only in the right upper quadrant of the abdomen. There was marked local tenderness over the liver.

Second, in regard to the presence of abnormal vasomotor reaction or faulty respiration, I can only state that the subjects were not of any single body type. It is common knowledge that the incidence of the stitch pain is so high that it could hardly be limited to those with the ptotic body type. In contradistinction to Nassau and Kugelmass, I found that deep breathing usually increased the pain rather than gave relief. Although they claimed that breathing exercises prevent the attacks, one is not justified in concluding that abnormal respirations cause visceral distention. Their observations are susceptible of a different interpretation; namely, a change in breathing habits might simply

13. Nassau.[3] Kugelmass.[4]

14. Jones, C. M.: Digestive Tract Pain, New York, The Macmillan Company, 1938.

alter the load on the diaphragm. Finally, acute heart failure is readily eliminated as a probable factor, since relatively mild exercise in trained athletes may precipitate the pain.

It is thus evident that none of the previously proposed explanations of this pain are satisfactory. There is another possible cause that, so far as I know, has never been suggested, namely, anoxemia of the diaphragm. This explanation, which was first suggested to me by Dr. George H. Coleman, satisfies, I believe, all of the requirements in a much more satisfactory manner than any other.

The reference of pain from the muscular portion of the diaphragm is not definitely established. Gill and McArdle [15] reported 2 cases of hysteric spasm of the diaphragm without pain. Porter [16] described a case and reviewed the literature of diaphragmatic flutter with distribution of pain like that in angina pectoris. The consensus is that the pain in such cases arises in organs other than the diaphragm and is brought about only by reflexes arising from abnormal diaphragmatic action. These observations throw little light on the distribution of pain referred from the diaphragmatic muscle. It is known, however, that the pleura and peritoneum which overlie the muscular portion of the diaphragm refer pain to the lower intercostal nerves.[17] It is not unreasonable to suppose that these same fibers may refer pain from the underlying muscle. Furthermore, the blood supply of the diaphragm is intimately associated with the intercostal arteries, and afferent vegetative fibers running with the vasomotor nerves might well refer pain to the intercostal nerves connecting with the same or an adjacent spinal segment. This distribution of pain corresponds closely to that observed in the stitch.

Actual physical exertion is obviously necessary to produce anoxemia, and this might vary with the physical condition of the subject, with the type of breathing, with the state of being "warmed up" and with the postprandial condition. Cold weather would be expected to affect the diaphragm much as it does the heart in cases of angina pectoris or the leg muscles in cases of intermittent claudication. This also holds true of eating. Deep breathing would be expected to increase the pain, as it was frequently found to do. Holding the breath, although it stops diaphragmatic contractions, also increases anoxia, so that it would have variable effects. Bending over, especially toward the affected side, and local pressure both act to limit diaphragmatic motion and so would be

15. Gill, W. G., and McArdle, M. J.: Two Cases of Pseudo-Tympanites Caused by Hysterical Spasm of the Diaphragm, Guy's Hosp. Rep. **84**:94, 1934.

16. Porter, W. B.: Diaphragmatic Flutter with Symptoms of Angina Pectoris, J. A. M. A. **106**:992 (March 21) 1936.

17. Capps, J. A.: An Experimental and Clinical Study of Pain in the Pleura, Pericardium and Peritoneum, New York, The Macmillan Company, 1932.

expected to give relief of stitch pain, even though physical exertion were continued. This effect on diaphragmatic motion of bending over has been confirmed by Dr. Hollis E. Potter [18] by actual observation of the diaphragm under the fluoroscope. One other observation also offers strong corroborative evidence. I have frequently observed both in myself and in others a pain in every way identical with the side ache which is brought on by strenuous and prolonged laughter, especially after a large meal. Laughing is accompanied by a series of rapid contractions of the diaphragm, often without adequate respirations. Possibly in excessive laughter there is a spasm of the diaphragm, as it may become difficult to draw a deep breath. Such a pain is probably identical with the side ache of exercise in that it arises from the diaphragmatic muscle. Perhaps this is the origin of the term "side-splitting" laughter.

Why the pain is generally unilateral is not entirely clear. It is natural that one side should be affected first, and perhaps the person stops exercising before the other side begins to hurt. Finally, it should be pointed out again that the observations of Nassau and Kugelmass are on the whole consistent with this explanation of the mechanism of the pain. Improved breathing might well put less of a load on the diaphragm.

SUMMARY

1. One hundred and fourteen attacks of side ache occurring in 55 persons have been personally observed and the important features analyzed.

2. The outstanding characteristics are found to be a constant relation to exertion, a tendency to occur after eating, a variable location, usually in either the right or the left upper quadrant of the abdomen, relief obtained from bending over or from local pressure and a tendency to be aggravated in cold weather.

3. The previously proposed theories regarding the mechanism of pain are shown to be untenable. A new explanation of the pain is suggested, namely, anoxemia of the diaphragmatic muscle. This theory explains all of the observed facts in an entirely satisfactory manner.

Assistance was given by the coaches and athletic directors at the University of Chicago High School, the University of Chicago and Northwestern University.

18. Potter, H. E.: Personal communication to the author.

VITAMIN A AND CAROTENE CONTENT OF HUMAN LIVER IN NORMAL AND IN DISEASED SUBJECTS

AN ANALYSIS OF ONE HUNDRED AND SIXTEEN HUMAN LIVERS

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The vitamin A content of the liver has been reported by several observers,[1] but as a variety of methods were used for the determination of vitamin A and as many of these methods have since been shown to have a wide margin of error, the majority of the results are qualitative rather than quantitative. An exception to this is the report by Crimm and Short,[2] in which the livers of 7 healthy persons were found to have an average vitamin A content of 33,100 U. S. P. units per hundred grams of liver. In a later study [3] they reported that in 50 patients with tuberculosis the average vitamin A content of the liver was 34,200 U. S. P. XI units per hundred grams. In 14 of the patients, however, the vitamin A content of the liver was low. Occasional scattered reports of both the vitamin A and the carotene contents of human livers may be found,[4] but there are no large series of cases in which the concentrations of these two substances in human livers have been observed. As the source of vitamin A in the diet under ordinary circumstances is carotene, which

From the Department of Medicine, New York University College of Medicine.

1. Moore, T.: Distribution of Vitamin A and Carotene in the Body of the Rat, Biochem. J. **25**:274, 1931; Vitamin A Reserves of Human Liver in Health and Disease, Lancet **2**:669, 1932. Fox, F. W.: Vitamin A in Livers of Native Miners, ibid. **1**:953, 1933. Wolff, L. K.: On the Quantity of Vitamin A Present in the Human Liver, ibid. **2**:617, 1932.

2. Crimm, P. D., and Short, D. M.: Vitamin A Content of Human Liver, Am. J. M. Sc. **189**:571, 1935.

3. Crimm, P. D., and Short, D. M.: Vitamin A Content of the Human Liver in Tuberculosis, Ann. Int. Med. **13**:61, 1939.

4. Pariente, A. C.; Present, C. H., and Ralli, E. P.: A Case of Carotenemia and Diabetes Mellitus with Necropsy Report and Analyses of Liver for Carotene, Vitamin A, Total Fat and Cholesterol, Am. J. M. Sc. **192**:365, 1936. Flaum, G., and Stueck, G. H., Jr.: Hemochromatosis: Report of a Case with Necropsy and Analysis of the Liver, Arch. Int. Med. **63**:433 (March) 1939.

must be converted by the liver to vitamin A before it is utilized by the body, it seemed to us that the concentration of these two substances in the liver and their relationship to each other were of interest.

In this study the livers of 116 persons were analyzed. The material was obtained at autopsy.[5] Twenty-five of the subjects were healthy persons who were killed in accidents. The remaining 91 suffered from various diseases and are divided into groups according to the clinical diagnoses and pathologic findings. Vitamin A was determined after extraction[6] in the Hilger vitameter. Carotene was determined on the same extract in the photoelectric colorimeter.[7] Samples of the liver were obtained in most cases within twenty-four hours after death.

RESULTS OF ANALYSIS

GROUP I: *No Disease* (25 subjects; table 1).—The material in this group was derived from persons who had been killed in accidents and in whom no gross pathologic condition was observed at autopsy except the immediate cause of death. Of these persons, 20 were males and 5 were females. The ages varied from 4 to 81 years.

The average vitamin A content of the liver of these normal subjects was 121,000 U.S.P. units per hundred grams of wet liver. There was a considerable range, as can be seen in the table, but in 18 of the normal subjects the vitamin A content of the liver was above 40,000 U. S. P. units per hundred grams and in 8 it was above 100,000 U.S.P. units. The average vitamin A content of the liver in this series of normal subjects is four times as high as the average value reported by Crimm and Short (33,100 U. S. P. units per hundred grams of liver). As 18 of the normal livers in our series had a vitamin A concentration above 40,000 U. S. P. units per hundred grams of liver and as Crimm and Short analyzed only 7 normal livers, it seems to us that the value they obtained is at the lower level of normal. As will be seen in the other tables, in many of the livers of the patients with disease the amount of vitamin A was appreciably reduced. The lowest vitamin A content of the liver in this normal group was that for patient 100 (3,400 U. S. P. units), in whom both the vitamin and the carotene were so low as to suggest a low dietary intake.

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5. The samples of liver were obtained for analysis through Dr. Douglas Symmers, director of the department of pathology of Bellevue Hospital, and through the Department of Hospitals and the office of the Chief Medical Examiner, New York.

6. Davies, A. W.: The Colorimetric Determination of Vitamin A by the Alkali Digestion Method, Biochem. J. **27**:1770, 1933.

7. Stueck, G. H., and Ralli, E. P.: The Application of the Photoelectric Colorimeter to the Determination of Carotene in Blood Serum, Liver and Feces, Am. J. Physiol. **119**:411, 1937.

The average carotene content of the normal livers was 1.44 mg. per hundred grams of wet liver. The range was from 0.33 to 3.71 mg. per hundred grams. The latter value, which is high, was found in the case of a 4 year old child and was accompanied by an unusually high concentration of vitamin A, undoubtedly reflecting a high dietary intake of carotene. The difference in the proportion of carotene to vitamin A may be due to the fact that in the infant the liver may not convert carotene as rapidly to vitamin A as does the liver in the adult. Clausen [8] has shown that carotenemia is not at all uncommon in young children,

TABLE 1.—*Analysis of Livers from Twenty-Five Persons Without Gross Pathologic Conditions*

Case No.	Nutritional State of Subject	Age	Sex	Weight of Liver, Gm.	Vitamin A, U. S. P. Units per 100 Gm.	Carotene, Mg. per 100 Gm.	Vitamin A / Carotene × 10^{-3}
8	Fair	50	M	1,500	177,900	2.30	77
12	Fair	30	M	1,250	79,700	1.60	50
15	Good	10	M	950	130,000	1.40	93
16	Good	74	F	1,200	43,700	1.37	38
17	Good	35	M	1,300	197,800	1.20	165
4	Good	34	M	1,760	44,400	3.90	11
35	Good	45	M	1,630	95,500	1.96	48
47	Fair	30	M	1,820	72,900	0.43	169
49	Good	55	M	1,800	13,700	2.37	6
59	Good	40	M	1,670	23,600	0.97	24
69	Good	59	F	1,370	39,100	1.46	27
60	Good	55	M	1,780	46,200	0.45	103
61	Good	18	F	1,200	60,000	1.21	49
63	Good	14	M	1,100	60,400	1.32	46
71	Good	62	M	1,500	77,300	0.50	155
72	Good	55	M	1,620	234,200	0.91	257
76	Good	4	M	530	635,000	3.71	171
77	Good	35	F	1,170	55,900	1.64	34
80	Fair	39	M	1,500	114,900	2.52	45
81	Good	49	M	1,450	639,000	0.97	650
85	Good	35	M	1,650	16,900	0.35	48
89	Fair	45	M	1,470	25,200	0.33	76
90	Fair	81	M	1,410	134,900	1.56	86
94	Good	50	M	1,540	13,300	1.28	104
100	Fair	39	F	1,300	3,400	0.41	8
Average.....		42	..	1,430	121,000	1.44	84

and the increase in the blood may reflect an accumulation in the liver. The only other subject with as large a concentration of vitamin A in the liver was a 49 year old man (case 81), but the amount of carotene in the liver of this subject was 0.97 mg. per hundred grams of liver, which value indicates that in the normal adult liver the tendency is for carotene to be converted to vitamin A and to be stored as such. The proportion of vitamin A to carotene in the liver was calculated in an effort to determine whether these two substances bore any consistent relation to each other. The range of the ratio was large, with an average of 84×10^{-3}. Any significance that can be attached to this ratio is a

8. Clausen, S. W.: Limits in Anti-Infective Value of Pro-Vitamin A (Carotene), J. A. M. A. **101**:1384 (Oct. 28) 1933.

relative one and is brought out by comparing the ratio for the groups of diseased patients with that for the group of normal persons (table 5). Although in all of the former groups there is less vitamin A in proportion to the amount of carotene, when the ratios are compared the value for E shows that the difference is significant only for the group of patients with cirrhotic livers.

TABLE 2.—*Analysis of the Livers from Twenty-Six Patients with Acute and Chronic Alcoholism*

Case No.	Nutritional State of Patient	Age	Sex	Weight of Liver, Gm.	Vitamin A, U. S. P. Units per 100 Gm.	Carotene, Mg. per 100 Gm.	Vitamin A / Carotene × 10^{-3}	Pathologic Changes in the Liver and Other Disease Processes
56	Poor	35	F	2,450	7,800	0.23	34	Fatty liver; streptococcic meningitis
99	Good	35	M	1,780	15,000	1.24	12	Fatty liver
75	Poor	41	M	1,910	31,000	0.43	72	Lobar pneumonia; fatty liver
65	Good	40	F	1,750	21,000	2.26	9	Fatty liver
96	Good	45	M	1,450	47,100	0.38	129	Normal liver
82	Good	45	M	1,720	47,500	0.85	56	Pulmonary tuberculosis; fatty liver
66	Poor	50	M	1,410	146,000	2.23	65	Cardiac failure; normal liver
91	Fair	50	M	1,050	163,000	3.72	40	Slightly fatty liver
84	Good	38	M	1,850	31,300	0.77	41	Pulmonary tuberculosis
1	Good	..	M	2,350	58,300	1.80	32	Enlarged and fatty liver
25	Poor	68	F	1,450	35,700	0.40	89	Chronic passive congestion of liver; coronary thrombosis; ascites
28	Fair	50	M	1,800	47,100	0.64	74	Subdural hematoma
43	Good	..	F	1,500	31,900	0.60	53	
6	Fair	53	M	1,500	44,400	1.70	26	Coronary sclerosis
101	Fair	51	M	1,650	18,000	0.90	20	Fractured skull; cirrhosis of liver
102	Good	47	M	1,750	74,300	0.75	99	Enlarged heart, chronic passive congestion of liver
103	Poor	55	M	2,550	56,800	0.15	379	Hypernephroma; no metastases into liver
58	Poor	50	M	1,950	13,900	1.32	10	Pneumonia; cirrhosis
110	Good	47	M	4,000	900	0.07	13	Fatty liver; ascites; jaundice; cirrhosis
111	Fair	47	M	2,950	53,800	1.07	50	Fatty liver; ascites; jaundice; cirrhosis
113	Poor	39	M	3,500	5,300	0.00	5	Hemochromatosis; diabetes; ascites; cirrhosis
112	Poor	65	M	1,450	4,600	0.14	33	Portal cirrhosis; ascites
114	Poor	49	F	1,600	8,700	0.75	12	Cirrhosis; ascites; jaundice
115	Poor	24	F	1,700	0	0.58	0	Cirrhosis; ascites; jaundice
116	Poor	39	F	1,150	6,300	0.41	15	Cirrhosis; pulmonary tuberculosis; ascites; jaundice
39	Fair	62	M	3,300	4,900	0.05	98	Fatty liver; periportal fibrosis; cirrhosis
Average.....				1,980	37,500	0.90	57	

GROUP II: *Alcoholism* (26 patients; table 2).—This group consists of patients with a history of chronic alcoholism, some of whom were in a state of acute alcoholism when admitted to the hospital. In many of these patients other diseases, not directly the result of alcoholism, were also found, as is indicated in the table. Five of the patients were deeply jaundiced and had ascites. Ascites was also present in 3 other patients. There were 10 patients in whom cirrhosis of the liver was noted. In 12 patients the liver weighed more than 1,750 Gm.

In 16 patients the vitamin A concentration of the liver was below 40,000 U. S. P. units per hundred grams of liver, and in 9 of these it was below 15,000 U. S. P. units. The average for the group was 37,500 U. S. P. units per hundred grams of liver, which is the low limit of normal if both our results and those of Crimm and Short are considered. Although the average carotene value for this group was only slightly lower than that for the normal one, when it is considered in relation to the vitamin A value for the normal group the ratio is two-thirds that for the normal group. The low vitamin A content of the liver of these

TABLE 3.—*Analysis of the Livers from Fifteen Patients with Cirrhosis of the Liver*

Case No.	Nutritional State of Patient	Age	Sex	Weight of Liver, Gm.	Vitamin A, U. S. P. Units per 100 Gm.	Carotene, Mg. per 100 Gm.	Vitamin A / Carotene × 10^{-3}	Pathologic Changes in the Liver and Other Disease Processes
58	Poor	50	M	1,950	13,900	1.32	10	Alcoholism; lobar pneumonia; fatty liver; cirrhosis
39	Fair	62	M	3,300	4,900	0.05	98	Alcoholism; fatty liver; cirrhosis
13	Good	82	M	1,300	39,700	0.90	44	Arteriosclerotic heart disease; cirrhosis
31	Good	38	M	1,650	16,900	0.92	18	Lobar pneumonia; fatty liver; cirrhosis
98	Good	65	M	1,600	13,900	0.76	18	Cardiac failure; chronic passive congestion and cirrhosis of liver
58	Good	55	F	.....	8,200	....	..	Cirrhosis of liver
101	Fair	51	M	1,650	18,000	0.90	20	Alcoholism; fractured skull; cirrhosis
106	Poor	26	F	1,880	10,700	0.15	71	Cardiac failure; cirrhosis
110	Good	47	M	4,000	900	0.07	13	Fatty liver; alcoholism; ascites; jaundice; cirrhosis
113	Poor	39	M	3,500	5,300	0.00	..	Alcoholism; hemochromatosis; ascites; cirrhosis
111	Fair	47	M	2,950	53,800	1.07	50	Alcoholism; fatty liver; jaundice; ascites; cirrhosis
112	Fair	65	M	1,450	4,600	0.14	33	Alcoholism; ascites; cirrhosis
114	Poor	49	F	1,600	8,700	0.75	12	Cirrhosis; alcoholism; ascites; jaundice
115	Poor	24	F	1,700	0	0.58	0	Cirrhosis; alcoholism; ascites; jaundice
116	Poor	39	F	1,150	6,300	0.41	15	Cirrhosis; pulmonary tuberculosis; alcoholism; ascites; jaundice
Average.....				2,120	13,700	0.57	31	

patients with alcoholism probably is due both to an inadequate dietary intake and to some hepatic dysfunction resulting either from the accumulation of fat in the liver or from cirrhosis. The factor which would be most likely to interfere with the storage of vitamin A or with the conversion of carotene to vitamin A would be some pathologic change in the liver, such as cirrhosis.

GROUP III: *Cirrhosis of the Liver* (15 patients; table 3).—In this table we have grouped the patients with cirrhosis of the liver. Ten of the 15 patients had a history of alcoholism. In 7 patients ascites was present. The livers were fatty in 5 patients, 4 of whom had a history of alcoholism.

The vitamin A content of the liver was strikingly lowered in all but 2 cases in this group, and in 1 of these the cirrhosis was described after microscopic examination as early. In the 13 remaining cases the vitamin A content was 18,000 U. S. P. units per hundred grams or below. The carotene value for the group was also lower than normal, and the carotene/vitamin A ratio averaged 31 $\times$ 10^{-3}, which when compared with the ratio for the normal group gave a significant value for E of 4.4. Both the lowered content of vitamin A in the liver and the decrease in the proportion of carotene to vitamin A point to the importance of normal hepatic tissue in the storage and the metabolism of these substances. As was mentioned before, with the destruction of normal hepatic cells the ability to store vitamin A is reduced and the conversion of carotene to vitamin A is interfered with.

TABLE 4.—*Summary of Results of Analyses of Livers from Normal Persons and from Patients with Various Diseases*

Disease	Number of Livers Analyzed	Average Weight of Liver, Gm.	Vitamin A, U. S. P. Units per 100 Gm.	Carotene, Mg. per 100 Gm.	Vitamin A / Carotene $\times 10^{-3}$
None	25	1,430	121,000	1.44	84
Alcoholism	26	1,980	37,500	0.90	57
Cirrhosis	15	2,120	13,700	0.57	31
Acute infections without pathologic condition of the liver	16	1,760	45,400	0.95	63
Acute infections with pathologic condition of the liver	6	1,835	24,600	0.58	61
Chronic infections	10	1,760	38,300	0.79	59
Metabolic diseases	12	1,740	72,300	1.35	54
Malignant conditions	7	1,780	74,900	1.32	57
Cardiovascular diseases	16	1,540	58,300	1.37	43

GROUP IV: *Acute Infections* (22 patients; table 4).—This group consists of patients in whom the cause of death was an acute infectious process. In 16 of the patients there was no associated cirrhosis or fatty infiltration of the liver. The vitamin A content of the liver was below 40,000 U. S. P. units per hundred grams of liver in 8 of the 16 patients, and the carotene content was lower than normal. The ratio of vitamin A to carotene was 63 $\times$ 10^{-3}. The vitamin A content was below 40,000 U. S. P. untis per hundred grams of liver in 5 of the 6 patients with cirrhosis or fatty infiltration of the liver, and the carotene was also reduced. The ratio of vitamin A to carotene was 62 $\times$ 10^{-3} for the entire group and thus again showed less vitamin A in proportion to the amount of carotene than is found in the normal liver.

GROUP V: *Chronic Infectious Diseases* (10 patients; table 4).—This group consists of patients dying of chronic infectious diseases. In 6 patients in this group the total vitamin A content of the liver was below

40,000 U. S. P. units per hundred grams of liver, and there was a corresponding reduction in the carotene content of the liver. The average carotene value for the group was 0.79 mg. per hundred grams of liver, with a range from 0.21 to 1.64 mg. These figures are at the lower limits of normal.

GROUP VI: *Metabolic Diseases* (12 patients; table 4).—This group consists of 8 patients with obesity which was complicated by some other pathologic process, 3 patients with diabetes mellitus and 1 patient with Paget's disease of the bones.

The vitamin A content of the liver was below 30,000 U. S. P. units in 3 of the obese patients, and in 2 of them the obesity was complicated

TABLE 5.—*Statistical Analysis*

Group	Disease	Vitamin A, U. S. P. Units per 100 Gm. of Liver		Carotene, Mg. per 100 Gm. of Liver		Vitamin A / Carotene × 10^{-3}	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
I	None	76,000	±62,500	1.56	±0.87	74	±32.0
II	Alcoholism	37,500	±40,300	0.90	±0.91	57	±74.0
III	Cirrhosis	13,700	±14,500	0.57	±0.49	31	±28.8
IV	Chronic infection	38,300	±16,000	0.79	±0.44	59	±46.3
V	Acute infection						
	(a) Without damage to the liver	45,400	28,100	0.95	0.57	63	47.0
	(b) With damage to the liver	24,000	225	0.56	0.45	61	55.0

	E : Vitamin A	E : Carotene	Vitamin A / E : Carotene × 10^{-3}
I and II	3.9	2.4	1.3
I and III	7.2	5.3	4.4
I and IV	4.1	3.8	1.2
I and V(a)	3.1	2.7	0.99
I and V(b)	6.0	4.6	0.08

by infection. The carotene content of the liver of patients in this group was within normal limits. The carotene contents of the liver of the 3 patients with diabetes were 0.85, 1.40 and 1.70 mg. per hundred grams of liver. The vitamin A contents of the livers of the patients with diabetes were 58,000, 59,000 and 75,000 U. S. P. units per hundred grams of liver.

GROUP VII: *Malignant Conditions* (7 patients; table 4).—In this group there were 4 cases of carcinoma, in 2 of which there were metastases to the liver. There was 1 case each of lymphosarcoma, leukemia and hypernephroma. In 5 cases the nutritional state was poor. In 6 cases the patient was over 55 years of age.

The vitamin A content of the liver was low in 3 of the 7 patients, with a corresponding reduction in the carotene content of the liver.

Curiously enough, the patient with lymphosarcoma, although emaciated, had a high value for both vitamin A and carotene. This patient had metastatic nodules in the liver, and the question arises whether these nodules may have stored vitamin A.

GROUP VIII: *Cardiovascular Diseases* (16 patients; table 4).—This group consists of patients with hypertensive, arteriosclerotic and syphilitic heart disease. Four of these patients had coronary thrombosis. In only 7 of the patients was the liver normal on pathologic examination. In 3 patients there was chronic passive congestion; in 3 patients the state of the liver was not reported, and in the remaining patients there was either cirrhosis or fatty infiltration. Ten of the patients had vitamin A values for the liver within normal limits. The average for the group was 58,300 U. S. P. units per hundred grams of liver. The value for carotene ranged from 0.76 to 3.30 mg. per hundred grams of liver. The average for the group was normal.

COMMENT

A summary of the findings for the various groups is given in table 4, which permits a comparison of the average results for each group. If one accepts the fact that the normal liver will contain at least 40,000 U. S. P. units of vitamin A per hundred grams of liver, the striking reductions in the concentration of this substance are found to occur in the patients with cirrhosis of the liver and in the patients with acute infections, who in addition showed some pathologic change in the liver, such as cirrhosis or fatty infiltration. Although the average vitamin A content of the liver of the patients with alcoholism and of those with chronic infectious disease does not show the same consistent reduction, in each of these groups there were many cases in which the vitamin A content of the liver was significantly lowered. It is particularly interesting to note that of the 16 patients with alcoholism who had a lowered vitamin A content of the liver, the condition in 11 was complicated by either cirrhosis of the liver or by infection.

The finding of a low concentration of vitamin A in these patients with cirrhosis of the liver is consistent with the observation of Patek and Haig [9] that patients with such a condition had impairment of dark adaptation.

The carotene content of the liver was significantly low in the same groups of patients, for example, those with cirrhosis and acute infections in which there was an associated pathologic change in the liver. The same general fact holds true for the averages for carotene as for the

9. Patek, A. J., Jr., and Haig, G.: Occurrence of Abnormal Dark Adaptation and Its Relation to Vitamin A Metabolism in Patients with Cirrhosis of the Liver, J. Clin. Investigation **18**:609, 1939.

averages for vitamin A, and the carotene values were low for those patients with alcoholism for whom the vitamin A content of the liver was low.

The objective analysis of the results of the vitamin A and the carotene determinations are shown in table 5. In calculating the standard deviations the average value for vitamin A for the normal group was taken as 76,600 instead of 121,000 U. S. P. units per hundred grams of liver. The former is the average value obtained when the figures for the 2 subjects (cases 76 and 81) with extremely high concentrations of vitamin A are omitted. The values for carotene were treated in the same way. The standard deviations are fairly large. This is to be expected, as the ages of these persons varied from the first decade to the eighth, the diets were an unknown factor and probably subject to considerable variation and the nutritional states of the subjects differed. However, when the average vitamin A content of the liver obtained in this group of normal persons is compared with the average content for the various groups of diseased patients, we find that the E value for vitamin A shows that the differences are significant in all groups. The same is true for carotene.

If one takes 40,000 U. S. P. units per hundred grams of liver as the normal vitamin A content of the liver, which would be indicated by Crimm and Short's results, significant differences as expressed by the E value occur only in the groups of patients with cirrhosis of the liver and with acute infections associated with damage to the liver. The ratio of vitamin A to carotene was significantly reduced only in the group of patients with cirrhosis of the liver. The importance of this ratio in the various groups is minimized, owing to the wide variation in each group. As mentioned before, we have previously suggested [10] that the ability of the liver to convert carotene to vitamin A may be interfered with under certain circumstances. Obviously, cirrhosis of the liver accompanied by severe damage to the liver might provide such a condition.

The fact that in the cases of acute infection in which there was also some pathologic change in the liver there was a significant reduction of vitamin A stresses the role of the liver as a storehouse of vitamin A. Previous reports have suggested that infection depletes the stores of vitamin A in the liver. The fact that in cases of acute infection associated with a pathologic condition of the liver the vitamin A and carotene

10. Ralli, E. P.; Pariente, A. C.; Brandaleone, H., and Davidson, E.: Effect of Carotene and Vitamin A on Patients with Diabetes Mellitus, J. A. M. A. **106**:1975 (June 6) 1936. Ralli, E. P.; Brandaleone, H., and Mandelbaum, T.: Studies on the Effect of the Administration of Carotene and Vitamin A in Patients with Diabetes Mellitus, J. Lab. & Clin. Med. **20**:1266, 1935.

contents of the liver were almost 50 per cent lower than in the cases of acute infection uncomplicated by any pathologic condition of the liver suggests that the pathologic condition of the liver is a more significant factor in maintaining the normal vitamin A stores of the liver than is infection per se. Probably the condition of the liver and the vitamin A content of the diet are the two most important factors in determining the concentration of the vitamin in the liver.

SUMMARY

The vitamin A and carotene contents of the livers of 116 subjects are reported. Twenty-five of the patients were normal persons as far as could be ascertained and served as a basis of comparison for the other groups.

In the patients with cirrhosis of the liver and in those with acute infection and an associated pathologic condition of the liver there was a striking decrease in the vitamin A and the carotene content of the liver. The ratio of vitamin A to carotene was significantly altered only in the group of patients with cirrhosis of the liver.

It is suggested that the factors that determine the vitamin A content of the liver are the dietary intake of vitamin A and the pathologic state of the liver. At present cirrhosis of the liver seems to be the most important pathologic disturbance.

HEMORRHAGIC DIATHESES

AN ANALYSIS OF THREE HUNDRED AND FIFTY-FIVE AUTOPSY REPORTS

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All too frequently the word purpura is used as a diagnosis. This is obviously unsound, since the word has been employed to describe anything from a minute petechia to gross capillary hemorrhage. Since purpura is derived from the Greek word *πορφυρα*, meaning "purple," its use should be limited purely to description.

The term hemorrhagic diathesis is more accurate than the older term purpura. It may be correctly applied to any extravasation of blood through the endothelial wall of the capillaries, regardless of amount. Hence, it includes not only the external, visible evidences of capillary damage, such as bleeding into the skin, the oral mucosa, the nasal mucosa or the conjunctiva, but also the hidden bleeding from the mucosa or the serosa of the internal organs.

Tidy [1] coined the term "angio-staxis" to include the "primary" purpuras and the various manifestations of the hemorrhagic states. However, there is no need for the introduction of a new term into an already confused nomenclature. Hemorrhagic diathesis, qualified by the phrase "on the basis of," is an accurate diagnostic and descriptive term.

CLASSIFICATION OF THE HEMORRHAGIC STATES

There are three factors that may be the precipitating cause of a hemorrhagic diathesis. These are:

1. Damage to or weakness of the capillary endothelium.
2. A deficiency of the clot-forming elements.
3. Faulty clot retraction, due to a decreased number of platelets.

These factors are used as the basis of the main divisions in the various classifications of the hemorrhagic states. Similar schemes are

From the Department of Medicine, Cook County Hospital.

1. Tidy, H. L.: Hemorrhagic Diathesis: Angio-Staxis, Lancet **2**:365, 1926.

followed by Downey,[2] Whitby and Britton,[3] Kracke and Garver,[4] Osler,[5] Mettier[6] and Peck, Rosenthal and Erf.[7] The essential difference in the various classifications lies only in the subgroups and smaller divisions of the three main etiologic types of abnormal bleeding.

The following classification which we have used in the analysis of our material differs only in its subdivisions from those referred to.

I. Hemorrhagic diatheses due to platelet deficiencies
- A. "Essential" thrombopenia (idiopathic thrombopenic purpura)
- B. Allergic thrombopenia
- C. Symptomatic thrombopenia—caused by bone marrow deficits
  1. Blood dyscrasias
  2. Multiple metastases to bone marrow
  3. Gaucher's disease and other lipoid dystrophies

II. Hemorrhagic diatheses due to changes in the capillary walls
- A. Anaphylactoid states
- B. Infectious states
  1. Acute infections
  2. Chronic infections
- C. Nephritic "toxins"
- D. Drug intoxications
- E. Vitamin deficiencies (C and P)

III. Hemorrhagic states due to changes in the clotting elements of the blood
- A. Diseases of the liver
  1. Atrophy of the liver
  2. Cirrhosis of the liver
  3. Obstructive jaundice
- B. Vitamin K deficiency
- C. Hemorrhagic disease of the newborn
- D. Icterus neonatorum
- E. Hemophilia

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2. Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 1.

3. Whitby, L. E. H., and Britton, C. J. C.: Disorders of the Blood, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1937.

4. Kracke, R. R., and Garver, H. E.: Diseases of the Blood and Atlas of Hematology, Philadelphia, J. B. Lippincott Company, 1937.

5. Osler, W.: Modern Medicine: Its Theory and Practice, Philadelphia, Lea & Febiger, 1908, vol. 4.

6. Mettier, S. R.: Classification and Treatment of the Hemorrhagic States, J. A. M. A. **108**:83 (Jan. 9) 1937.

7. Peck, S. M.; Rosenthal, N., and Erf, L.: Purpura: Classification and Treatment, Arch. Dermat. & Syph. **35**:831 (May) 1937.

ANALYSIS OF CASES

The material used in this analysis was obtained from the autopsy reports of the Cook County Hospital from 1929 to 1937. During this period 10,355 autopsies were performed. Of this number 355 revealed evidences of hemorrhagic diatheses, an incidence of 3.4 per cent. On the basis of the anatomic diagnosis, all cases in which there were hemorrhagic manifestations were investigated, and a correlation was attempted between the type of diathesis and its probable cause.

The classification we have given in the preceding section is one adapted to clinical use. The summary of the pathologic reports will include some, but not all, of the clinical types.

I. Hemorrhagic diatheses due to platelet deficiencies, 21.9%

A. Essential thrombopenia	6
B. Symptomatic thrombopenias	
1. Blood dyscrasias	
(*a*) Leukemias	39
(*b*) Aplastic anemia	12
(*c*) Hodgkin's disease	3
(*d*) Pernicious anemia	3
(*e*) Sickle cell anemia	2
(*f*) Hemolytic anemia	1
2. Multiple metastases to bone marrow	12

II. Hemorrhagic diatheses due to changes in the capillary walls

A. Infectious states, 49.3%	
1. Acute infections	
(*a*) Septicemia	14
(*b*) Otitis media	3
(*c*) Meningitis	30
(*d*) Pneumonia	11
(*e*) Typhoid fever	2
(*f*) Endocarditis	96
(*g*) Gangrenous pharyngitis	1
(*h*) Pyonephrosis	4
2. Chronic infections	
(*a*) Tuberculosis	12
(*b*) Abscess of the lung	2
B. Toxins of nephritic origin, 16.3%	
1. Benign nephrosclerosis (associated with eccentric hypertrophy of the heart)	20
2. Malignant nephrosclerosis	16
3. Subacute and chronic glomerular nephritis	16
4. Acute glomerular nephritis	5
5. Mercury bichloride poisoning	1

III. Hemorrhagic states due to changes in the clotting elements of the blood
- A. Diseases of the liver, 7.3%
  - 1. Atrophy of the liver 4
  - 2. Cirrhosis of the liver 9
  - 3. Obstructive jaundice
    - (*a*) Common duct stone 2
    - (*b*) Adenocarcinoma of the biliary tract 5
  - 4. Toxic hepatitis 4
  - 5. Carcinoma with extensive metastases to the liver 2
- B. Hemorrhagic disease of the newborn, 1.4% 5
- Icterus neonatorum, 1.1% 4

IV. Unclassified hemorrhagic states, 2.5%
- A. Congenital syphilis 3
- B. Atelectasis 2
- C. Eclampsia 1
- D. Coronary thrombosis 2
- E. Waterhaus-Friedrichsen syndrome 1

It now becomes evident that in the differential diagnosis of bleeding states, essential thrombopenic purpura plays a minor role, accounting for only 1.7 per cent of all the cases. The blood dyscrasias themselves account for less than one fifth of the material. From our analysis, the most important cause of the hemorrhagic diatheses appears to be the infectious states, since they include up to 50 per cent of the entire series of cases. Among the infectious conditions, bacterial endocarditis is the greatest offender, causing 27 per cent of all the hemorrhagic diatheses. Next in importance is meningitis, which is encountered in 8.5 per cent of the material.

Ranking almost equally in importance with the blood dyscrasias as a cause of abnormal bleeding states are the hemorrhagic diatheses produced by toxins of nephritic origin. These include the nephroscleroses, both benign and malignant, and the glomerular nephritides of the acute, subacute and chronic varieties.

Accounting for 9.8 per cent of the total number of cases are those instances of hemorrhagic states associated with jaundice. The 1 case of hemolytic anemia has been included with the blood dyscrasias. In all cases the condition was dependent on some type of damage to the liver which, in addition to causing icterus, produced changes in the clotting elements of the blood plasma, with a resultant increase in the bleeding or clotting time.

Briefly summarized, the relative frequency of the factors in the production of the hemorrhagic states may be listed as follows:

1. Infectious diseases 49.3%
2. Platelet deficiencies 21.9%
3. Pathologic renal conditions 16.3%
4. Hepatic disorders 9.8%

CORRELATION OF PATHOLOGIC MANIFESTATIONS WITH ETIOLOGIC FACTORS

The mode of production of the hemorrhagic diatheses by the pathologic phenomena just listed is of great interest. We shall attempt to explain each anatomic cause of bleeding by references to similar cases reported and by an evaluation of the physiologic processes involved.

The hemorrhagic diatheses due to platelet deficiencies include the essential thrombopenia (idiopathic thrombopenic purpura) and the symptomatic thrombopenias. In all these conditions there is an actual reduction in the number of platelets in the circulating blood. The reduction in the number of platelets in essential thrombopenia may be due to an actual decrease in the number of megakaryocytes in the bone marrow, to a defect in the maturation of the megakaryocytes with a decreased extrusion of platelets [8] or to actual destruction of the platelets in the spleen.[9] The destruction of platelets in the spleen is the most plausible theory, since splenectomy is followed by a rapid increase in the number of platelets in the circulating blood. However, recent experimental studies have shown that there is a substance in the splenic tissue which is injurious to the megakaryocyte.[10] From this it may be assumed that platelets are restored after splenectomy by the removal of the platelet-inhibiting factor secreted by the spleen or by the removal of a substance which inhibits the maturation of the megakaryocytes.

The reduction in the number of platelets found in the symptomatic thrombopenias is due to a quantitative decrease in the number of megakaryocytes in the bone marrow or, again, to an inhibition of the substance effecting maturation of the megakaryocytes. Either of these factors would make for a decrease in the number of platelets in the circulating blood. The group of cases of hemorrhagic states due to changes in the capillary wall, next to be discussed, makes up the largest in our series, 233 of a total of 355, and the condition is caused by any factor which may tend to damage the wall of the vessels.

We have listed no cases in the anaphylactoid or allergic groups, despite the many reports in the literature concerning such conditions.[11]

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8. Frank, E.: Haemorrhagische Diathesen, in Klemperer, G., and Klemperer, F.: Neue deutsche Klinik, Berlin, Urban & Schwarzenberg, 1930, vol. 4, p. 395.

9. Kaznelson, P.: Erfahrungen über die Indikationen der Splenectomie und über deren Wirkungsmechanismus, Wien. Arch. f. inn. Med. **7**:87, 1923.

10. Torrioli, M., and Puddu, V.: Recent Studies on the Pathogenesis of Werlhof's Disease, J. A. M. A. **111**:1455 (Oct. 15) 1938. Troland, C. E., and Lee, F. C.: Thrombocytopen: Substance in Extract from Spleen of Patients with Idiopathic Thrombocytopenic Purpura That Reduces Number of Blood Platelets, ibid. **111**:221 (July 16) 1938.

11. Fox, M. J., and Enzer, N.: A Consideration of the Phenomenon of Purpura Following Scarlet Fever, Am. J. M. Sc. **196**:3, 1938. Ellis, R. W. B.: Allergic

(Footnote continued on next page)

In most of the cases in which the diathesis was reported as due to allergic reactions of the capillary wall the forerunner was an infectious or a toxic process which might well have been the etiologic agent in the injury of the capillary wall.

The infectious diseases, both acute and chronic, are the greatest offenders in the production of a weakened capillary wall and the resultant escape of the cellular elements of the blood stream. This damage to the capillary wall may be brought about in several ways. Bacterial emboli may lodge in the small bore capillaries. This results in a direct necrotic action on the vessel wall, as in bacterial endocarditis, generalized septicemias and typhoid fever. Damage to the wall may also be caused by weakening and breaking of the endothelial lining of the capillary due to the action of the toxins produced by the bacteria, as in pneumonia and meningitis.

Purpuric lesions have been noted in association with tuberculosis and are regarded as a poor prognostic sign in this disease.[12] Fishberg [13] expressed the belief that the presence of purpura in tuberculosis is merely a coincidence. However, both Cruice [12a] and Houcke and Boury [12b] suggested that the pathogenic factor in the purpuric eruption associated with tuberculosis is the absorption of toxins from rapidly breaking down tuberculous foci. Since both conditions are met with in the terminal stages of tuberculosis, the presence of a hemorrhagic diathesis in the course of a tuberculous infection may be viewed as evidence of increased activity of the tubercle bacillus.

The presence of a hemorrhagic diathesis of nephritic origin must always be kept in mind in the differential diagnosis of the hemorrhagic states. Fisher [14] was the first to suggest that toxins might be present in the blood of persons with nephritic disease. These toxins, by means of a destructive action on the capillary endothelium, might be capable of causing hemorrhagic extravasations. Riesman [15] held that the bleeding was due either to the hypertension which is usually present or to toxemia. He drew attention to the serious prognostic significance of a

Purpura, Proc. Roy. Soc. Med. **31**:768, 1938. Stoesser, A. V., and Lockwood, W. W.: Varicella Complicated with Acute Thrombocytopenic Purpura and Gangrene, J. Pediat. **12**:641, 1938.

12. (*a*) Cruice, J. M.: The Incidence of Purpura in the Course of Chronic Pulmonary Tuberculosis, Am. J. M. Sc. **144**:875, 1912. (*b*) Houcke, E., and Boury, M.: Purpura et tuberculose pulmonaire, Sang **12**:44, 1938.

13. Fishberg, M.: Pulmonary Tuberculosis, Philadelphia, Lea & Febiger, 1932.

14. Fisher, T.: Haematemesis Associated with Small White Kidneys, Bristol Med.-Chir. J. **22**:243, 1904.

15. Riesman, D.: Hemorrhages in the Course of Bright's Disease, with Special Reference to the Occurrence of a Hemorrhagic Diathesis of Nephritic Origin, Am. J. M. Sc. **134**:709, 1907.

hemorrhagic diathesis in nephritis. The most plausible cause of a hemorrhagic state in nephritis is the retention of nitrogenous products and the occurrence of uremia,[16] which exert a damaging effect on the capillaries of the entire body.

Of interest in the causation of a hemorrhagic diathesis by toxins of nephritic origin is an incidental observation by Drury.[17] In the course of experiments on the production of renal insufficiency in rabbits, he noted hemorrhages in the intestinal wall and bleeding into the lumen of the intestinal tract at autopsy.

The purpuric manifestations occurring in acute nephritis are most likely due to toxemia of streptococcic origin and as such are distinct from those caused by the chronic forms of nephritis.

Several of our cases in which there was only a slight nitrogen retention (up to 50 mg. of nonprotein nitrogen per hundred cubic centimeters of blood) were included with those of the hemorrhagic diatheses due to toxins of nephritic origin. The patients in all of these cases had an elevation of blood pressure of over 150 mm. of mercury systolic. The occurrence of a bleeding tendency in those patients may be explained by the findings of Levrat and Ballivet.[18] They found that of 7 persons without hypertensive disease, over 60 years of age, only 1 gave a positive reaction to a tourniquet test, while of 33 persons with proved hypertension, 4 of whom were under 50 years of age, all but 2 showed a positive reaction to a tourniquet test. They postulated that the factor involved in the production of the purpuric eruptions was mechanical, due to an increased arterial pressure transmitted to the capillaries, or was based on an increased capillary fragility.

The 1 case of mercury bichloride poisoning which we included in our series may be explained by the marked nitrogen retention produced by the action of mercury on the kidney.

Before leaving the hemorrhagic states which are due to changes in the capillary wall, it may be fitting to mention the effect of vitamin C. It has long been known that the presence of vitamin C in the diet is of importance in the prevention of scurvy. The scorbutic states are manifested by bleeding from the gums, into the skin and subperiosteally. That vitamin C is necessary in the maintenance of the integrity of the capillary wall has been shown in many ways. Roberts and his

16. Davidson, L. S. P.; Davenport, C., and Rabagliati, D. S.: Discussion on Purpuric Conditions in Man and Animals, Proc. Roy. Soc. Med. **30**:715, 1937. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1939, pp. 182 and 672.

17. Drury, D. R.: Renal Insufficiency and Hypertension, J. Exper. Med. **68**: 693, 1938.

18. Levrat, M., and Ballivet, J.: Le purpura provoqué chez les hypertendus, Lyon méd. **163**:243, 1939.

associates [19] estimated the capillary fragility in children with the Dalldorf resistometer. They found a distinct seasonal change in the capillary fragility, which became greatest at the time when vitamin C was lowest in the diet. Liebmann and his co-workers [20] attempted to correlate the capillary fragility with the vitamin C content of the blood. They found a 70 to 75 per cent agreement between the level of vitamin C in the blood and the result of the Rumpel-Leeds tourniquet test.

More recently, Szent-Györgyi and his associates [21] have brought forth the claim that vitamin P (pure citrin—$C_{28}H_{36-38}O_{17}$) is concerned with the maintenance of normal permeability of the capillaries. Jersild [22] reported the cure of a patient with Schönlein-Henoch purpura by the use of citrin itself.

The hemorrhagic conditions due to changes in the clotting elements of the blood are all dependent on underlying pathologic changes in the liver and an increase in the prothrombin time of the blood. The absence of adequate amounts of the antihemorrhagic factor in the diet and the faulty absorption of vitamin K through the intestinal mucosa are causes of abnormal bleeding which have only recently been emphasized.[23]

We have included 35 cases of hemorrhagic diatheses associated with jaundice. Of these, 7 were cases of obstructive jaundice in which there was a lack of absorption of vitamin K due to the absence of bile from the intestine. With this absence there occurs a lowering of the level of prothrombin in the blood.[24] In the presence of severe hepatic disease, such as atrophy, cirrhosis, hepatitis and extensive carcinomatous

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19. Roberts, L. J.; Blair, R., and Bailey, M.: Seasonal Variation in Capillary Resistance of Institution Children, J. Pediat. **11**:626, 1937.

20. Liebmann, J.; Wortis, H., and Wortis, E.: Note on Lack of Correlation of Capillary Fragility with Vitamin C Content of Blood, Spinal Fluid and Urine, Am. J. M. Sc. **196**:388, 1938.

21. Rusznyák, S., and Szent-Györgyi, A.: Vitamin P.: Flavonals as Vitamins, Nature, London **138**:27, 1936. Szent-Györgyi, A.: Sur la vitamine P, Bull. Acad. de méd. de Roumanie **2**:17, 1937. Bentsáth, A.; Rusznyák, S., and Szent-Györgyi, A: Vitamin P, Nature, London **139**:326, 1937. Vitamin P, editorial, J. A. M. A. **114**:43 (Jan. 6) 1940.

22. Jersild, T.: Therapeutic Effect of Vitamin P in Schönlein-Henoch Purpura, Lancet **1**:1445, 1938.

23. Clark, R. L.; Dixon, C. F.; Butt, H. R., and Snell, A. M.: Deficiency of Prothrombin Associated with Various Internal Disorders: Its Treatment with the Antihemorrhagic Vitamin (Vitamin K), Proc. Staff Meet., Mayo Clin. **14**:26, 1939.

24. Dam, H., and Glavind, J.: Vitamin K in Human Pathology, Lancet **1**:720, 1938. Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: Hemorrhagic Tendency in Jaundice (Obstructive) and Biliary Fistula, Am. J. M. Sc. **196**:50, 1938.

deposits, there is a derangement in the metabolism of prothrombin. This in turn causes a hemorrhagic tendency, due to the inability of the blood elements to form thrombin.

The same factors also operate in hemorrhagic disease of the newborn, as shown by Waddell and Guerry,[25] and are the cause of the bleeding tendency in jaundice of the newborn.

There remain 9 cases which we have been unable to classify. The 3 cases of congenital syphilis may possibly be explained by a weakening of the capillary wall caused by the syphilitic infection. The 2 cases of coronary thrombosis which were accompanied by hemorrhagic lesions may be explained by the concomitant hypertension and consequent weakening of the capillary wall, as was earlier hypothesized.

The 2 cases of atelectasis which we encountered present a more difficult problem. Perhaps the hemorrhagic state may here be due to the concomitant anoxemia, which is characterized by minute hemorrhages into the submucosa and the subendothelial areas. Again, it may be a manifestation of the hypoprothrombinemia from which some newborn and older infants suffer.

The purpuric manifestations seen in the case of eclampsia may be due to the hepatic damage produced by the toxemia.

In the case of the Waterhaus-Friedrichsen syndrome the classic changes of hemorrhage into the adrenal glands and of purpuric spots in the skin were presented. Whether this was due to an underlying sepsis or to a congenital weakness of the capillary bed cannot be ascertained at present.

SUMMARY

1. The scope of the term "hemorrhagic diathesis" is defined.

2. The hemorrhagic diatheses are classified on the basis of physiologic alterations in the blood and in the vessel walls.

3. The pathologic manifestations of the hemorrhagic diatheses are correlated with the etiologic factors.

25. Waddell, W. W., and Guerry, Du P., III: Effect of Vitamin K on the Clotting Time of the Prothrombin and the Blood, J. A. M. A. **112**:229 (June 3) 1939.

TREATMENT OF LOBAR PNEUMONIA WITH RABBIT ANTIPNEUMOCOCCUS SERUM

EFFICACY OF THE PROJECTED DOSE METHOD OF TREATING PNEUMONIA WITH HOMOLOGOUS REFINED AND UNCONCENTRATED RABBIT ANTIPNEUMOCOCCUS SERUM

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During the past year pneumococcic pneumonia was treated almost exclusively with chemotherapeutic substances. Pneumonia during this period was relatively mild, and bacteremia was infrequent. A decreased mortality rate for pneumonia, which could not be attributed entirely to specific measures, was noted. We feel, therefore, that a study of the results obtained with a specific therapeutic agent during a previous period in which pneumonia was known to be more severe and in which there was a higher incidence of bacteremia should be presented at this time.

Rabbit antipneumococcus serum was first used by Horsfall, Goodner and MacLeod [1] in 1936. In 1937, these authors and an associate [2] described 22 cases in which this serum was used. In 1938, the first three authors reported the results obtained with homologous serum in 67 cases of types I, II, III, V, VI, VII, VIII, XIV and XVIII pneumococcus pneumonia in which the mortality rate was 3.7 per cent when 13 cases of type III pneumococcus pneumonia were excluded.[3]

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1. Horsfall, F. L., Jr.; Goodner, K., and MacLeod, C. M.: Type Specific Antipneumococcus Rabbit Serum, Science **84**:579 (Dec. 25) 1936.

2. Horsfall, F. L., Jr.; Goodner, K.; MacLeod, C. M., and Harris, A. H., Jr.: Antipneumococcus Rabbit Serum as Therapeutic Agent in Lobar Pneumonia, J. A. M. A. **108**:1482 (May 1) 1937.

3. Horsfall, F. L., Jr.; Goodner, K., and MacLeod, C. M.: Antipneumococcus Rabbit Serum as Therapeutic Agent in Lobar Pneumonia: Additional Observations in Pneumococcus Pneumonias of Nine Different Types, New York State J. Med. **38**:245 (Feb. 15) 1938.

In 1938, we reported 69 cases of types I, II, V, VII, VIII and XIV pneumococcus pneumonia treated with homologous refined and unconcentrated rabbit antipneumococcus serum.[4] In this series the mortality rate was 7.4 per cent. In 1939, we reported a series of 125 cases of types V, VII and VIII pneumococcus pneumonia in which only 2.4 per cent of the patients died.[5]

Wood,[6] in 1939, published a report of 50 cases of types I, II, III, IV, V, VI, VII, VIII and XIV pneumococcus pneumonia in which treatment was with rabbit antipneumococcus serum and in which the mortality rate when 8 cases of type III pneumococcus pneumonia were excluded was 14.3 per cent.

Volini and Levitt,[7] in 1939, studied twenty-one types of pneumonia in 153 cases in which rabbit antipneumococcus serum was used and in which the corrected mortality rate was 7.2 per cent.

It is the purpose of our present paper to summarize the studies made in 320 cases of types I, II, V, VII, VIII and XIV pneumococcus lobar pneumonia treated with homologous refined and unconcentrated rabbit antipneumococcus serum.

METHODS AND MATERIAL

Antipneumococcus Serums.—The rabbit antipneumococcus serum used in treatment in these cases was unconcentrated but refined, having been prepared according to the methods of Goodner, Horsfall and Dubos.[8]

Cases.—From December 1937 to April 1939 inclusive, the cases of 320 patients with pneumonia were studied in the pneumonia service of the Long Island College Hospital and the medical services of the Kings County Hospital. Many of the patients had received no medical treatment prior to their admission to the hospital. The study was based on an unselected consecutive series of cases. The cases of 8 patients were excluded from the analysis of results for the following reasons: One patient had a type V pneumococcus acute bacterial endocarditis at the time of admission to the hospital. Another patient had a Streptococcus viridans subacute bacterial endocarditis and a terminal type VII pneumococcus pneumonia.

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4. Loughlin, E. H.; Bennett, R. H., and Spitz, S. H.: Treatment of Lobar Pneumonia with Rabbit Antipneumococcus Serum: Preliminary Report, J. A. M. A. **111**:497 (Aug. 6) 1938.

5. Loughlin, E. H.; Bennett, R. H., and Spitz, S. H.: Treatment of Types V, VII and VIII Pneumococcus Pneumonia with Rabbit Antipneumococcus Serum, New York State J. Med. **39**:18 (Sept. 15) 1939.

6. Wood, W. B., Jr.: Treatment of Pneumococcic Pneumonia with Concentrated Antipneumococcus Rabbit Serum, J. A. M. A. **111**:745 (Aug. 26) 1939.

7. Volini, I. F., and Levitt, R. O.: Treatment of Pneumococcic Pneumonia with Concentrated Rabbit Serum, J. A. M. A. **113**:1314 (Sept. 30) 1939.

8. Goodner, K.; Horsfall, F. L., Jr., and Dubos, R. J.: Type Specific Antipneumococcic Rabbit Serum for Therapeutic Purposes: Production, Processing and Standardization, J. Immunol. **33**:279 (Oct.) 1937.

In both cases, at autopsy, the endocarditis was found to be the primary cause of death. Another patient had a cerebral hemorrhage prior to admission and died within five hours after serum treatment was started. The remaining patients, moribund on admission, died between three and ten hours after serum therapy was begun. The cases of patients who lived more than twelve hours after they received the first dose of serum were included in the analysis.

Typing.—The sputum was cultured, and the typing of pneumococci, which was done according to the Neufeld method, was confirmed by mouse inoculation. When satisfactory specimens of sputum could not be obtained, culture of material from the lung was made.

Blood cultures were made prior to administration of serum and usually at intervals of twenty-four hours during the febrile period.

Examinations.—When the patient was admitted to the hospital, the history was taken and a physical examination and studies of the blood were made. The diagnosis was confirmed roentgenologically.

The Francis test was made in a number of cases prior to and during serum therapy, and at times it was used to determine the necessity of additional serum. The clinical appearance of the patient, however, generally determined the course of therapy.

Sensitivity Tests.—Intravenous: One tenth of a cubic centimeter of rabbit antipneumococcus serum diluted to 5 cc. with physiologic solution of sodium chloride was injected into a vein. The blood pressure and the heart rate were determined just prior to, and five minutes after, the injection of this test dose of serum. The patient was considered sensitive to rabbit serum if there was a fall in blood pressure of 20 mm. of mercury or an increase in the heart rate of twenty beats per minute.

Conjunctival: One tenth of a cubic centimeter of a 1:10 dilution of rabbit serum was dropped into a conjunctival sac. Sensitivity of the patient to the serum was manifested by itching, lacrimation, congestion, and swelling of the conjunctiva.

Dosage of Rabbit Antipneumococcus Serum.—In August 1938, we reported the cases of 69 patients, to each of whom a predetermined or projected dose of rabbit antipneumococcus serum was given; of these, 40 were successfully treated with a single dose.[4]

In September 1939,[5] we reported the cases of 125 patients, and of these, 102 were successfully treated with a single projected dose.

To all the patients whose cases are reported in this present paper, a projected dose of rabbit serum was administered. This is the quantity of serum, measured in Felton units, that we have found adequate to produce a crisis in the average case of pneumococcic lobar pneumonia.

Determination of Dose: When a patient was less than 40 years of age, had been ill less than sixty hours, had involvement of no more than one lobe and had neither complications nor bacteremia, 160,000 units was given in cases of types I, V and VIII pneumococcus pneumonia, while in cases of types II, VII and XIV pneumococcus pneumonia 200,000 units was given. However, in January, February, March and April, because of the high incidence of infections of the respiratory tract, diminished resistance on the part of the patients and the increased virulence of the pneumococci, 200,000 units was administered in cases of types I, V and VIII pneumococcus pneumonia and 260,000 units in cases of types II, VII and XIV pneumococcus pneumonia.

When a patient was over 40 years of age, had been ill more than sixty hours, had involvement of more than one lobe and had complications or bacteremia, 200,000 units was given in cases of types I, V and VIII pneumococcus pneumonia, while in cases of types II, VII and XIV pneumococcus pneumonia 300,000 units was given. An additional 60,000 units in cases of types I, V and VIII pneumococcus pneumonia and 100,000 units in cases of types II, VII and XIV pneumococcus pneumonia was given during January, February, March and April.

Leukopenia, particularly in cases of type VIII pneumococcus pneumonia, indicated to us the probability of bacteremia. When leukopenia was noted, the projected dose considered necessary in a case of bacteremia was given.

Subsequent doses of serum, when necessary, were usually administered at intervals of twenty-four hours. The quantity was determined by the clinical condition of the patient, the presence or absence of bacteremia, the response to the previous dose and, at times, the results of the Francis test. We used the pulse rate and the respiratory rate as clinical guides for determining the necessity of further therapy. When either remained elevated, more serum was given.

Administration of Rabbit Antipneumococcus Serum.—When a patient was found not to be sensitive to rabbit antipneumococcus serum, the projected dose of serum was administered intravenously. From 10 to 15 grains (0.6 to 1 Gm.) of acetylsalicylic acid was given orally just prior to the administration of the serum and before each subsequent dose.

A syringe containing a solution of epinephrine hydrochloride (1:1,000) was always available at the bedside. Heat was never applied to the serum, which preferably was warmed in the hands or was allowed to stand until it reached room temperature.

The cuff of the sphygmomanometer was placed around the arm other than the one into which the serum was to be given. The serum was administered with an intravenous drip infusion set. A physiologic solution of sodium chloride was allowed to flow into the vein and after the rate was regulated, the administration of the serum was begun. When the level of the serum had reached the outlet of the infusion flask, an additional 25 to 50 cc. of physiologic solution of sodium chloride was poured into the flask to insure complete utilization of the serum in the tubing.

The pulse rate was observed during the administration of serum. When there was a significant increase in the rate or when the patient presented reactions which were considered anaphylactoid or anaphylactic, the flow of serum was temporarily discontinued and a determination of blood pressure made.

When there was no decrease in the blood pressure, the administration of serum was allowed to continue. However, when a decrease in blood pressure of 20 mm. of mercury or more was noted, 1 or 2 minims (0.06 to 0.12 cc.) of a solution of epinephrine hydrochloride (1:1,000) was injected into a vein. When the blood pressure had returned to the previous level, the serum was then permitted to flow very slowly.

RESULTS

Pneumonia Due to Pneumococcus Type I.—One hundred and twenty-six patients with type I pneumococcus pneumonia were treated with type I refined and unconcentrated rabbit antipneumococcus serum (chart 1, table 1). In 53 cases there was consolidation of two or more lobes, and in 13 bilateral consolidation was found. Thirty-four patients had bacteremia. The pneumonia had been present for an average of

ninety-five hours, with extremes of fifteen hours and two hundred and forty hours, before rabbit serum was administered. Ninety patients had pneumonia seventy-two hours or more before treatment (chart 2). The average amount of serum given was 316,000 units. The temperature fell to normal in an average of fourteen hours, with extremes of two hours and ninety-two hours.

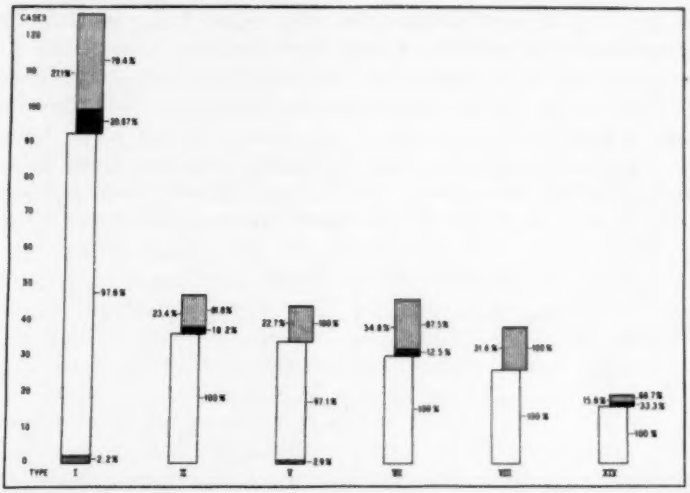

Chart 1.—Incidence of bacteremia (percentage at left of column) and survival and death (percentage at right of column) in 320 cases of pneumococcic pneumonia treated with homologous rabbit antipneumococcus serum. The markings of each column signify the following conditions: vertical lines, bacteremia present, outcome favorable; solid black, bacteremia present, outcome fatal; solid white, bacteremia absent, outcome favorable, and cross-hatching, bacteremia absent, outcome fatal.

TABLE 1.—*Pneumococcic Pneumonia Treated with Homologous Rabbit Antipneumococcus Serum*

Type	Number of Cases	Bacteremia	Interval Between Onset and First Dose of Serum, Average (Hr.)	Total Dose of Serum, Average (Units)	Number of Successful Single Doses	Interval Between First Dose of Serum and Crisis, Average (Hr.)	Serum Sickness	Mortality, Percentage
I	126	24	95	316,000	100	11	41	7.1
II	47	11	94	350,000	35	20	23	4.3
V	44	10	89	312,000	35	14	9	2.3
VII	46	16	83	340,000	36	15	9	4.4
VIII	38	12	80	300,000	34	12	9	0.0
XIV	19	3	111	333,000	12	36	8	5.3
Total	320	86			252			
Average			92 hr.			18.5 hr.		
Percentage		27			79			4.7

One hundred patients, of whom 15 had bacteremia, were successfully treated with one dose of serum, and in these crisis occurred in an average of twelve hours. The average single successful dose was 257,000 units.

Serum sickness developed in 41 patients.

One hundred and seventeen patients recovered, and 9 died. The mortality rate for type I pneumococcus pneumonia was 7.1 per cent.

Pneumonia Due to Pneumococcus Type II.—Forty-seven patients with type II pneumococcus pneumonia were treated with type II refined and unconcentrated rabbit antipneumococcus serum (chart 1, table 1). Thirteen patients had consolidation of two or more lobes, and, of these, 5 had bilateral processes. Eleven patients had bacteremia. The onset of the pneumonia had occurred on an average of ninety-four hours, with extremes of sixteen hours and two hundred and sixty hours, before rabbit serum was administered. In 31 cases the pneumonia had been present seventy-two hours or more before treatment was begun (chart

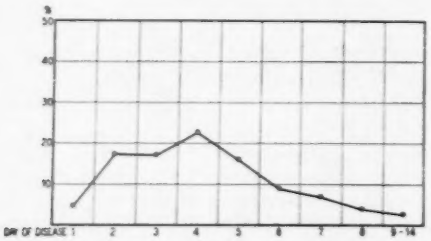

Chart 2.—Day of disease on which therapy with homologous rabbit antipneumococcus serum was begun in 320 cases of types I, II, V, VII, VIII and XIV pneumococcus pneumonia.

2). The average amount of serum given was 350,000 units. The temperature became normal in an average of twenty hours, with extremes of four hours and one hundred and twenty hours.

Thirty-five patients, of whom 8 had bacteremia, were successfully treated with one dose of serum. In these patients crisis occurred in an average of ten hours. The average single successful dose was 260,000 units.

Serum sickness developed in 23 cases.

Forty-five patients recovered, and 2 died. The mortality rate for type II pneumococcus pneumonia was 4.3 per cent.

Pneumonia Due to Pneumococcus Type V.—Forty-four patients with type V pneumococcus pneumonia were treated with type V refined and unconcentrated rabbit antipneumococcus serum (chart 1, table 1). Thirteen patients had consolidation of two or more lobes, and 8 of these

had bilateral involvement. Bacteremia was found in 10 cases. The pneumonia had been present for an average of eighty-nine hours, with extremes of twenty-six hours and one hundred and ninety-two hours, before rabbit serum was administered. Twenty-nine patients were treated after the pneumonia had been present seventy-two hours or more (chart 2). The average amount of serum given was 312,000 units. The temperature fell to normal in an average of fourteen hours, with extremes of three hours and forty-eight hours.

Thirty-five patients, of whom 7 had bacteremia, were successfully treated with one dose of serum, and in them crisis occurred in an average of nine hours. The average single successful dose was 231,000 units.

Serum sickness developed in 9 patients.

Forty-three patients recovered, and 1 died. The mortality rate for type V pneumococcus pneumonia was 2.3 per cent.

Pneumonia Due to Pneumococcus Type VII.—Forty-six patients with type VII pneumococcus pneumonia were treated with type VII refined and unconcentrated rabbit antipneumococcus serum (chart 1, table 1). In 19 cases there was consolidation of two or more lobes; while in 7 bilateral consolidation was found. Sixteen patients had bacteremia. The pneumonia had been present for an average of eighty-three hours, with extremes of twenty hours and one hundred and ninety-two hours, before rabbit serum was administered. Thirty patients had pneumonia seventy-two hours or more before treatment (chart 2). The average amount of rabbit serum given was 340,000 units. The temperature became normal in an average of fifteen hours, with extremes of two hours and ninety-six hours.

Thirty-six patients, of whom 7 had bacteremia, were successfully treated with one dose of serum. In these, crisis occurred on the average in ten hours. The average single successful dose was 279,000 units.

Serum sickness developed in 9 cases.

Forty-four patients recovered, and 2 died. The mortality rate for type VII pneumococcus pneumonia was 4.4 per cent.

Pneumonia Due to Pneumococcus Type VIII.—Thirty-eight patients with type VIII pneumococcus pneumonia were treated with type VIII refined and unconcentrated rabbit antipneumococcus serum (chart 1, table 1). Nineteen of them were admitted to the service with consolidation of two or more lobes, and 10 of these had bilateral consolidation. Twelve patients had bacteremia. The pneumonia had been present for an average of eighty hours, with extremes of fifteen hours and three hundred and thirty-six hours, before rabbit serum was administered. In 22 cases the pneumonia had been present seventy-two hours or more before treatment (chart 2). The average amount of

rabbit serum given was 300,000 units. The temperature fell to normal in an average of twelve hours, with extremes of three hours and forty-eight hours.

Thirty-four patients, of whom 9 had bacteremia, were successfully treated with one dose of serum. In these patients crisis occurred in an average of ten hours. The average single successful dose was 269,000 units.

Serum sickness developed in 9 cases.

Thirty-eight patients recovered, and none died. Thus the mortality rate for type VIII pneumococcus pneumonia was 0 per cent.

Pneumonia Due to Pneumococcus Type XIV.—Nineteen patients with type XIV pneumococcus pneumonia were treated with type XIV refined and unconcentrated rabbit antipneumococcus serum (chart 1, table 1). Five patients had consolidation of two or more lobes, and 3 of these had bilateral consolidation. Three patients had bacteremia. The pneumonia had been present for an average of one hundred and eleven hours, with extremes of thirty hours and one hundred and ninety hours, before rabbit serum was administered. In 16 cases the pneumonia had been present seventy-two hours or more before treatment was started (chart 2). The average amount of rabbit serum given was 333,000 units. The temperature fell to normal in an average of thirty-six hours, with extremes of eight hours and one hundred and twenty hours.

Twelve patients were successfully treated with one dose of serum, and in these crisis occurred in an average of twenty-three hours. The average single successful dose was 263,000 units.

Serum sickness developed in 8 patients.

Eighteen patients recovered, and 1 died. The mortality rate for type XIV pneumococcus pneumonia was 5.3 per cent.

COMPLICATIONS AND PREEXISTING DISEASES

Empyema occurred in 23 cases, and in 6 it was present at the time of admission to the hospital. Surgical drainage was required in 11 cases. Serum therapy produced spontaneous resolution in 8 cases. In 4 cases there was a fatal outcome.

Of those cases in which there were complications, delirium occurred in 20, jaundice in 10, noninfected pleural exudate in 16, otitis media in 7, meteorism in 7, pulmonary edema in 5, multiple pulmonary abscesses in 2, pulmonary atelectasis in 2, pericarditis in 2, meningismus in 4, circulatory collapse in 3 and gastroenteritis in 1.

There were preexisting diseases in 75 cases. Heart failure due to various causes occurred in 20, arteriosclerosis in 2, coronary occlusion in 2, hypertension in 2, uremia in 5, cystitis in 1, tuberculosis in 11, asthma in 7, bronchiectasis in 1, emphysema in 1, syphilis in 12, Hodgkin's disease in 1, diabetes in 2, diabetic acidosis in 1, hyper-

TABLE 2.—*Analysis of Deaths*

Sex	Race	Age	Lobes Involved	Bacteremia	Preexisting Diseases and Complications	Interval Between Onset and First Dose of Serum, Hours	Total Dose of Serum, Units	Number of Doses	Comment
					Type I				
M	N	27	Right upper, right lower	+	Multiple pulmonary abscesses	126	200,000	1	
M	N	49	Left upper, left lower	+	Meteorism	94	340,000	2	Meteorism uncontrollable
M	W	62	Right upper, right lower	+	Arteriosclerosis of coronary arteries; auricular fibrillation	168	200,000	1	
M	W	40	Left upper, left lower	0	Empyema; pericarditis; uremia	76	540,000	3	
M	W	67	Right upper, right middle, right lower	+	Hypertensive heart disease; auricular fibrillation; uremia; jaundice; empyema	72	1,080,000	3	Survival for 8 days after first dose of serum; death apparently from preexisting diseases
F	W	38	Right upper, right middle	+	Delirium	100	800,000	2	Death from massive pulmonary collapse 4 days after first dose of serum
F	W	45	Right lower	+	.....	70	200,000	1	Temperature normal for 36 hr. after first dose of serum; sudden death
M	W	58	Left upper, left lower	0	Multiple pulmonary abscesses; coronary occlusion	104	300,000	1	Death apparently from coronary occlusion
M	W	65	Left lower	+	General arteriosclerosis; empyema; uremia	60	600,000	2	
					Type II				
M	W	43	Right lower, right middle	+	Pulmonary edema	146	300,000	1	Death from circulatory failure which was present when patient admitted to hospital
M	W	54	Right lower	+	Empyema	168	800,000	4	
					Type V				
F	N	35	Right lower	0	Hyperthyroidism; thyroid crisis	120	540,000	2	Death apparently from thyroid crisis
					Type VII				
M	N	62	Right upper, right middle, right lower	+	Jaundice; delirium	96	500,000	2	
M	W	62	Right upper	+	Obesity; arteriosclerosis of coronary arteries; pulmonary edema	144	400,000	1	
					Type XIV				
F	W	45	Left lower	+	.....	120	400,000	1	

thyroidism in 2, pregnancy in 4, cirrhosis of the liver in 1, anemia in 2, purpura haemorrhagica in 1, atrophic arthritis in 1, fractures in 4, epilepsy in 1 and delirium tremens in 2.

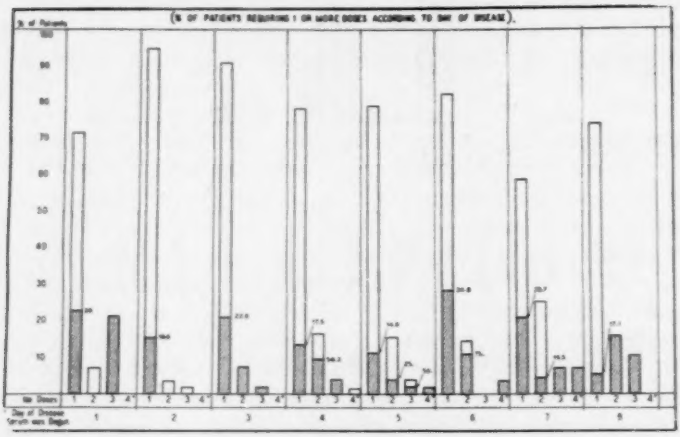

Chart 3.—Number of doses of homologous rabbit antipneumococcus serum required in 320 cases of types I, II, V, VII, VIII and XIV pneumococcus pneumonia. The diagonal lines and the figure at the right of each column represent the percentage of incidence of bacteremia.

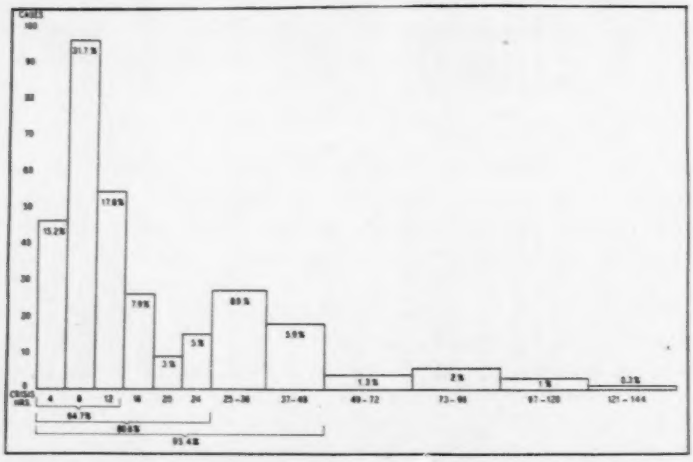

Chart 4.—Three hundred and three cases of types I, II, V, VII, VIII and XIV pneumococcus pneumonia in which recovery was by crisis.

ANALYSIS OF DEATHS

The 15 deaths are analyzed in table 2.

ANALYSIS OF RESULTS

It was possible to administer safely to each of the 320 patients a projected dose of refined and unconcentrated rabbit antipneumococcus serum. Two hundred and fifty-two, or 79 per cent, were successfully treated with this single predetermined dose (chart 3), and bacteremia was controlled in all but 3.

A rapid return to normal of the temperature, the pulse rate and the respiratory rate was usually observed, and of the 303 patients who recovered by crisis, 64.7 per cent had a normal temperature within twelve hours after serum therapy was begun and 80.6 and 95.4 per cent had normal temperatures within twenty-four and forty-eight hours respectively (chart 4).

No patients died when treated during the first two days of the disease, whereas the mortality rates in those first treated on the third, fourth, fifth, sixth and seventh days, were 7.5, 5.6, 5.9, 6.9 and 8.7 per cent respectively.

The mortality rate for the 320 patients, including 86 with bacteremia, was 4.7 per cent. In the group with bacteremia, there were 12 deaths: 7 from type I pneumococcus pneumonia, 2 from type II, 2 from type VII, and 1 from type XIV. The mortality rate of the patients with bacteremia was 13.9 per cent.

In the group without bacteremia, there were 3 deaths: 2 from type I pneumococcus pneumonia and 1 from type V. The mortality rate for the patients without bacteremia was 1.3 per cent.

Serum Reactions.—Chills following the administration of the rabbit serum occurred in 63 per cent of the cases. Although in a few instances such reactions were severe, they were never alarming. A rise of temperature, usually of 2 or 3 degrees (F.), followed the chills. This occurred generally after the first or second dose. The severity and the likelihood of occurrence diminished with subsequent doses. The occurrence and severity of the chills apparently were not dependent on the quantity or lot of serum used. Patients receiving large doses had chills no more frequently and no more severely than those receiving smaller doses. All patients receiving serum of the same lot did not have chills.

In a few instances anaphylactoid symptoms were noted. These were mild and did not cause alarm.

In 1 case the heart rate rose, the blood pressure fell 30 mm. of mercury and urticaria developed. In another case circulatory collapse occurred during the administration of the serum. After the intravenous injection of 2 minims (0.12 cc.) of epinephrine hydrochloride solution (1:1,000), the blood pressure returned to its previous level and serum therapy was continued. In 8 cases urticaria occurred during or shortly after the administration of serum.

Serum sickness developed in 31 per cent of the cases and was attended by the usual manifestations of fever, urticaria and arthritis. There were no instances of circulatory collapse during serum sickness.

SUMMARY AND COMMENT

Refined and unconcentrated rabbit antipneumococcus serum was found by us to be relatively nontoxic and effective in the treatment of types I, II, V, VII, VIII and XIV pneumococcus pneumonia.

When a projected dose was administered, an abundant supply of antipneumococcic substances was always made immediately available to the patient. A single projected dose produced a crisis in 252 (79 per cent) of the 320 cases. One hundred and ninety-six (65 per cent) and 244 (81 per cent) respectively of the 303 patients that recovered by crisis had normal temperatures within twelve and twenty-four hours after starting serum therapy.

The patients in our series were studied during periods when pneumonia was severe and when the incidence of bacteremia was high. The mortality rates obtained by us with rabbit antipneumococcus serum were lower than the majority of those for patients with milder pneumonia treated recently with chemotherapeutic substances.

Finland, Lowell and Strauss [9] analyzed the deaths among their drug-treated patients according to seasons. The mortality rate for 382 patients treated with sulfapyridine, including those treated with serum, in the season of 1939-1940 was 12.6 per cent, whereas the mortality rate for 354 patients treated during the season of 1938-1939 was 20 per cent.

The mortality rate for our group of 320 patients treated with serum from Dec. 1, 1937, to April 30, 1939, although including 27 per cent with bacteremia, was 4.7 per cent. The mortality rate for the patients with bacteremia was 13.9 per cent, and for those without bacteremia, 1.3 per cent.

Flippin, Schwartz and Reinhold [10] and Finland, Lowell and Strauss [9] have reported large series of cases in which treatment with chemotherapeutic agents yielded satisfactory results. Flippin and associates stated that serum was used in those cases in which treatment with a drug failed to bring about a satisfactory clinical response within thirty-six to forty-eight hours. They felt that the serum was a deciding factor in the recovery of several patients. Finland and co-workers used specific

9. Finland, M.; Lowell, F. C., and Strauss, E.: Some Aspects of Chemotherapy of Pneumonia, New York State J. Med. **40**:1115 (July 15) 1940.

10. Flippin, H. F.; Schwartz, L., and Reinhold, J. G.: Sulfapyridine and Sulfathiazole Therapy in Pneumococcic Pneumonia, J. A. M. A. **116**:683 (Feb. 22) 1941.

serum for the patients with severe pneumonia who were treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and sulfathiazole (2-[sulfanilamido]-thiazole).[9]

In view of these facts, we feel that rabbit antipneumococcus serum plays a definite part in the treatment of pneumococcic pneumonia and should not be discarded as an obsolete therapeutic agent until the chemotherapeutic agents are proved equally efficacious during periods of severe pneumonia when there is a high incidence of bacteremia. The treatment of pneumonia in the future, however, will probably progress to the combined use of drugs and specific serum.

Drs. Joseph K. Bradford, Duncan Clark, John Conley, Robert Dickes, Henry Gardstein, Philip Grenley, Ernest E. Keet, Catherine D. Mangan, Albert H. Meyer, David Rabinowitz and Sanford Sarney gave clinical assistance.

Anne M. Smith, Dora Zuckerman and J. Blitstein gave technical assistance.

Dr. Wade W. Oliver and Dr. Arnold Eggerth, of the Department of Bacteriology, Long Island College of Medicine, cooperated with us in this study.

The members of the staffs of the hospital named, notably Drs. Tasker Howard, J. Hamilton Crawford, Henry Moses, George Roberts, Henry Wolfer, George Sheehan, George H. Merrill and Arthur Frankhauser, permitted us to treat patients in their services with unconcentrated and refined rabbit antipneumococcus serum.

Progress in Internal Medicine

METABOLISM AND DIABETES

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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GLYCOGEN AND CARBOHYDRATE METABOLISM

In last year's review the importance of the work of Cori and his associates [1] on the synthesis of glycogen in vitro by the action of an enzyme called phosphorylase was pointed out. Phosphorylase, which is found in liver and muscle extracts and in yeast, acts on dextrose and phosphoric acid in the presence of adenylic acid, which acts as a coenzyme. Cori proceeded further in this investigation and in a recent paper [2] outlined the steps in the metabolism of glycogen as follows: 1. Glycogen plus phosphoric acid in the presence of the glycogen phosphorylase found in liver and other tissue yields dextrose-1-phosphate. This is a reversible reaction. 2. Dextrose-1-phosphate in the presence of phosphoglucomutase, an enzyme which is found in all tissue extracts, yields dextrose-6-phosphate. This reaction is irreversible. 3. Dextrose-6-phosphate in the presence of isomerase, an enzyme which is found in all tissue extracts, yields fructose-6-phosphate. Cori further stated that when this particular reaction has reached a state of equilibrium, the two esters are present in the proportion of 80 per cent dextrose and 20 per cent fructose. Such a mixture is known as hexosemonophosphate, or equilibrium ester. 4. Dextrose-1-phosphate or dextrose-6-phosphate when added to liver extract yields dextrose and inorganic phosphate through the action of phosphatase in the liver. These steps, Cori stated, are those taken in the formation of blood sugar.

From the Division of Medicine (Dr. Rynearson), the Mayo Clinic.

1. Cori, C. F.; Schmidt, G., and Cori, G. T.: The Synthesis of a Polysaccharide from Glucose-1-Phosphate in Muscle Extract, Science **89**:464-465 (May 19) 1939. Cori, G. T.; Cori, C. F., and Schmidt, G.: The Rôle of Glucose-1-Phosphate in the Formation of Blood Sugar and Synthesis of Glycogen in the Liver, J. Biol. Chem. **129**:629-639 (Aug.) 1939.

2. Cori, C. F.: Symposium on Carbohydrate Metabolism: Glycogen Breakdown and Synthesis in Animal Tissues, Endocrinology **26**:285-296 (Feb.) 1940.

Results of this series of investigations suggested that the enzymes concerned in the breakdown and the synthesis of glycogen in the liver and elsewhere play a fundamental role in carbohydrate metabolism. According to Cori, such an enzymatic breakdown leads to the formation of blood sugar in the liver and of lactic acid in muscle. In addition, various substances, including insulin, epinephrine, adrenocortical hormone, the active principles of the adrenal cortex and of the anterior lobe of the pituitary gland and possibly the sex hormones, influence enzyme activity in the cells and may thus play an important role in carbohydrate metabolism.

Janes and Nelson [3] reported that the administration to rats of 0.05 mg. of stilbestrol twice daily for five to twenty days resulted in elevation of the level of blood sugar and considerable rise in the glycogen content of the liver, although the glycogen content of muscle was not similarly increased. They expressed the opinion that both fat and protein serve as sources of the additional carbohydrate and that the stilbestrol might have produced such an effect through the adrenal glands, the gonads or both.

Studies on the effect of the adrenal glands, particularly the adrenal cortex, on carbohydrate metabolism have been numerous in the past few years. Recently, Long and his co-workers [4] stated:

> The injection of cortical extract or certain crystalline steroids isolated from the adrenal cortex into fasted adrenalectomized and normal rats and mice elevates the liver glycogen from ten to forty fold, resulting in levels far beyond those encountered in normal untreated animals. The blood glucose is also significantly increased, but no effects were observed on the muscle glycogen level.

They further reported that in depancreatized animals, the quantity of sugar in the urine, previously reduced by adrenalectomy, could be increased by cortical extract. They found a similar "diabetogenic" effect of cortical extract on fasting hypophysectomized depancreatized rats. Corticosterone and dehydrocorticosterone were found to exert marked effects on both carbohydrate and electrolyte metabolism, while desoxycorticosterone and progesterone, although capable of influencing both the duration of life and the electrolyte balance of adrenalectomized animals, had only a comparatively feeble effect on carbohydrate metabolism. They concluded that the "cortical hormone stimulates those processes of gluconeogenesis by which the blood glucose is maintained at the expense of the tissue proteins."

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3. Janes, R. G., and Nelson, W. O.: Effect of Stilboestrol on Certain Phases of Carbohydrate Metabolism, Proc. Soc. Exper. Biol. & Med. **43**:340-342 (Feb.) 1940.

4. Long, C. N. H.; Katzin, B., and Fry, E. G.: The Adrenal Cortex and Carbohydrate Metabolism, Endocrinology **26**:309-344 (Feb.) 1940.

On the other hand, Seckel [5] reported that glycogenolysis in the liver of rats, as it proceeded in sliced tissue suspended in a buffered salt solution, was inhibited by adrenal cortex extract added in vitro. He concluded that one essential function of the cortical hormone could consist in inhibition of the glycogenolytic enzyme of the liver cells. Furthermore, Russell [6] reported that in normal rats fed dextrose both whole anterior pituitary extract and adrenal cortical extract appeared to depress the utilization of carbohydrate and to promote deposition of glycogen. The former increased the muscle glycogen, and the latter more markedly affected the stores in the liver. She concluded that anterior pituitary extract and adrenal cortex extract have a synergistic, as well as, in part, a complementary, action on the metabolism of dextrose fed to rats.

Controversy continues with regard to the disturbance in carbohydrate metabolism primarily concerned in diabetes mellitus. Soskin [7] supported the so-called overproduction theory. He stated that in diabetes the ketone bodies as well as the blood sugar are capable of utilization by the extrahepatic tissue, but that they are produced by the liver at rates which exceed the power of the tissue to dispose of them. He [7] reported that the completely depancreatized dog receiving a constant injection of insulin sufficient to maintain a normal level of blood sugar has a normal dextrose tolerance curve, including the Straub-Traugott phenomenon and the hypoglycemic phase. On the other hand, a hepatectomized dog with an intact pancreas which received a constant injection of dextrose sufficient to maintain a normal level of blood sugar invariably has a diabetic tolerance curve. From these results, he concluded that the pancreas is not essential to the metabolic reactions which determine the normal dextrose tolerance curve, while the normal liver is essential. In the presence of sufficient insulin, the normal liver, as one of its responses to administered dextrose, decreases the output of sugar to the blood, which it had previously been supplying from its own resources. The stimulus which elicits the hepatic inhibitory response is the blood sugar itself, and the threshold of stimulation of the hepatic mechanism in a particular animal depends, Soskin claimed, largely on the endocrine balance. This balance may consist of the opposing influences of the hormones of the pancreas and the anterior lobe of the pituitary. When

5. Seckel, H. P. G.: The Influence of Various Physiological Substances on the Glycogenolysis of Surviving Rat Liver: Influence of Cortical Hormone Added in Vitro, Endocrinology **26**:97-101 (Jan.) 1940.

6. Russell, J. A.: The Relationship of the Anterior Pituitary and the Adrenal Cortex in the Metabolism of Carbohydrate, Am. J. Physiol. **128**:552-561 (Feb.) 1940.

7. Soskin, S.: The Liver and Carbohydrate Metabolism, Endocrinology **26**: 297-308 (Feb.) 1940.

insulin is lacking or when an excess of anterior pituitary hormones is present, the liver threshold, or the blood sugar level at which the inhibitory response is manifested, rises, and hyperglycemia results. An excess of insulin or a deficiency of the anterior pituitary hormones, on the other hand, lowers the liver threshold, and hypoglycemia results. When both insulin and the anterior lobe of the pituitary are lacking, as in the Houssay animal, the diabetes is ameliorated, and most of the criteria of normal carbohydrate metabolism are fulfilled.

Thannhauser,[8] however, disagreed with Soskin's theory that increased glyconeogenesis in cases of diabetes is the primary reason for the disturbance. He stated that if this were true, all diabetic patients would exhibit an increased minimal excretion of nitrogen, since the additional carbohydrate would come, at least in part, from protein catabolism. He reported that in 4 cases of moderately severe diabetes in which a minimal nitrogen diet was employed the minimal excretion of nitrogen was normal even though insulin was temporarily omitted. In 3 cases of severe diabetes in which a similar diet was given, the minimal excretion of nitrogen was slightly increased; simultaneously, large concentrations of sugar, four to seven times more than the amounts anticipated from the increased figures for the minimal excretion of nitrogen, appeared in the urine. Irradiation of the pituitary gland produced only a slight and temporary depression of the minimal excretion of nitrogen, while injection of extracts of whole pituitary and of adrenal cortex had no influence at all. Thannhauser concluded that the primary disturbance in diabetes mellitus consists in a partial failure of the molecule of sugar to be disintegrated in intermediary metabolism, that glyconeogenesis is the result of, and not the primary factor in, the mechanism of diabetes and that insulin does not act directly on glyconeogenesis but exerts its influence on the intermediary disintegration of sugar.

Several investigators emphasized the importance of stores of glycogen in the liver. Richardson [9] reported that in both normal rabbits and depancreatized cats survival after intravenous inoculation with bacteria was increased by high carbohydrate diets, which raised the glycogen content of the liver. Dissemination of bacteria from an intradermal focus in depancreatized cats, he reported, seemed to be correlated with alterations in glycogen in the skin, was increased by acidosis and occurred with a greater frequency in diabetic cats than in control animals. On the other hand, this dissemination could not be correlated with

8. Thannhauser, S. J.: Studies on the Mechanism of Diabetic Disturbance Using the "Nitrogen Minimum Excretion" as a Measure of Glyconeogenesis, Endocrinology **26**:189-200 (Feb.) 1940.

9. Richardson, R.: Immunity in Diabetes: III. Relation of Tissue Glycogen and Blood Chemistry to Bacterial Dissemination, Antibody Formation and Survival After Infection in Diabetes, J. Clin. Investigation **19**:239-250 (Jan.) 1940.

alterations in the amount of sugar in the blood, cholesterol or protein in the serum or glycogen in the liver.

Messinger and Hawkins [10] reported that in dogs in which the liver had been damaged previously with sufficient arsphenamine to produce jaundice, a diet high in carbohydrate or in protein aided in the restoration of hepatic function. Such a diet given before or during the administration of arsphenamine protected the liver from damage.

DIABETES MELLITUS

Incidence and Mortality.—Discussions continue on the increase or decrease in the incidence of diabetes. The general consensus is that the incidence of diabetes mellitus actually is increasing throughout the world. Beek and Groen [11] published the results of a detailed study in regard to the mortality rate of diabetes mellitus in the Netherlands. It increased tremendously from 1903 to 1937; in 1903, 424 persons died of this disease, and in 1937, 1,637. During these years the total population increased from 5,500,000 to 8,500,000. At present the mortality rate of diabetes in the Netherlands is one of the highest in the world; in 1935 it was surpassed only by those in the United States, Prussia, the Union of South Africa and Denmark. This increase in the mortality rate of diabetes is in sharp contrast to the marked decrease in the general mortality rate in the Netherlands, which fell during the period from 1903 to 1937 from 15.58 per thousand to 8.78 per thousand. Beek and Groen considered the causes which may have contributed to this increase and, while recognizing that the improved diagnosis of the disease and other factors may have contributed, they concluded that the increase is real and not apparent. They questioned if this increase may not be attributable to improved standards of nutrition and to decreased amounts of physical exercise. This increase in the mortality rate has taken place almost exclusively among those more than 50 years of age. The mortality among younger persons has decreased with the use of insulin. The higher mortality rate found in the cities may be due to the proportionately higher percentage of Jews. Diabetes has increased not only as a principal cause of death but as a contributory cause or complication. The most common complications are cardiac disease, angina pectoris, apoplexy, furunculosis and gangrene. The mortality rate among diabetic patients with pulmonary tuberculosis has decreased greatly. The mortality rate of diabetes itself, as well as the mortality rate of

10. Messinger, W. J., and Hawkins, W. B.: Arsphenamine Liver Injury Modified by Diet, Protein and Carbohydrate Protective, but Fat Injurious, Am. J. M. Sc. **199**:216-225 (Feb.) 1940.

11. Beek, E. S., and Groen, J.: The Mortality from Diabetes Mellitus in the Netherlands: Medical-Statistical Study, Geneesk. bl. u. klin. en lab. v. d. prakt. **37**:187-225, 1939.

diabetic coma, has remained rather constant since 1936. More than 200 patients die of diabetic coma in the Netherlands every year.

Joslin [12] long has been interested in the incidence of diabetes in various parts of the world and in various parts of the United States. After a detailed study of the incidence of the disease in Arizona, he concluded that diabetes is universal and found no evidence that the incidence is less in Arizona than elsewhere. This observation is important because of the discussions in regard to the influence of the seasons on the severity of diabetes and its complications. Owens and Mills [13] studied this problem in Cincinnati. They divided the year into seven months of winter (October to April) and five months of summer and found that more diabetic patients were admitted to hospitals for treatment of arteriosclerotic conditions in the winter than in the summer. The number of diabetic patients admitted to hospitals in the winter for other than arteriosclerotic conditions did not vary significantly from the number admitted in the summer.

Gangrene far outranked all other sclerotic complications. Less than a third of the patients who were admitted to hospitals because of diabetes had sclerotic complications. Owens and Mills concluded that there was no evidence of seasonal effect on the severity of diabetes not complicated by sclerotic conditions. They cited the observations of Beard,[14] of Minneapolis, who found that in 95 per cent of cases of diabetic gangrene this complication developed during the winter months. According to them, Blotner and Fitz [15] of Boston and Paullin [16] of Atlanta, Ga., also agreed that the incidence of gangrene increased during colder weather. Owens and Mills also cited Joslin as expressing the belief that the factors which contributed to the higher incidence during the winter were poor hygiene of the feet, increased spasm of the vascular system and decreased blood flow. Pannhorst and Rieger [17] concluded that in spite of seasonal correlations diabetes mellitus cannot be regarded as a seasonal disorder. Escudera, cited by Ryberg,[18] stated that there was a striking difference

12. Joslin, E. P.: The Universality of Diabetes: A Survey of Diabetic Morbidity in Arizona, J. A. M. A. **115**:2033-2038 (Dec. 14) 1940.

13. Owens, L. B., and Mills, C. A.: Influence of Season on the Severity of Diabetes and Its Sclerotic Complications, Am. J. M. Sc. **199**:705-708 (May) 1940.

14. Beard, A. H.: Treatment of Gangrene in Arteriosclerotic Diabetes, Minnesota Med. **8**:436-439 (July) 1925.

15. Blotner, H., and Fitz, R.: On Diabetic Gangrene, with Particular Reference to the Value of Insulin in Its Treatment, Boston M. & S. J. **194**:1155-1162 (June 24) 1926.

16. Paullin, J. E., in discussion on papers of Warfield and Lemann, J. A. M. A. **89**:662 (Aug. 27) 1927.

17. Pannhorst, R., and Rieger, A.: Manifestierung des Diabetes und Jahreszeit, Ztschr. f. klin. Med. **134**:154-161 (May 21) 1938.

18. Ryberg, P. E.: Personal communication to the authors.

in the incidence of diabetes in the Argentine. The incidence is lower in the north, where the climate is stable, than in the south, where the climate is less stable. The impression that the low incidence of diabetes in the southern part of the United States is explained by incomplete statistics seems not to apply in the Argentine since the standards of medical practice in the northern part of that country are high.

The Department of Health of Pennsylvania [19] recently announced new regulations by which both cancer and diabetes become reportable diseases. Previously, diabetes was registered only at the time of death. This improved method of reporting, if applied in all states, would benefit statistical analyses materially.

The Metropolitan Life Insurance Company [20] reported that the mortality rate of diabetes in the United States has resumed an upward trend after a temporary rest. In the first part of 1940 there was an increase of 13 per cent over the same period for 1939. The mortality rate among patients less than 25 years of age is low, only 1 or 2 per hundred thousand. This low rate, of course, is due to the use of insulin. As a matter of fact, it is only among patients more than 65 years of age that the mortality rates have increased steadily and rapidly. Since the population as a whole includes a steadily increasing percentage of older persons, a correction should be made in the mortality rates for diabetes. When this correction is made, the rise in the mortality rate for all ages is much more moderate. Regardless of any such correction, the known incidence of the disease has increased much faster than the mortality rate. There are no exact figures, but there are probably 500,000 to 600,000 cases of diabetes in the United States. Some estimates are even higher, and it is not unlikely that at the end of the present decade the figure will reach 1,000,000. If the mortality rate was computed on the basis of the diabetic population, rather than on the basis of the general population, it would probably show a decrease. Statistics from the Baker Clinic computed on the former basis disclosed an improvement in the mortality rate among diabetic patients of practically every age group, especially among children. It is encouraging to know that the mortality rate of diabetic coma has been reduced greatly. Even the mortality rates of other conditions, such as gangrene, to which an older person with diabetes is particularly susceptible, have been decreased. Most diabetic patients die of another disease common to their age group, such as cardiovascular disease, cancer or pneumonia. Many deaths could be prevented by education of those persons who have a family history of diabetes and are themselves overweight.

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19. Cancer and Diabetes Made Reportable, Medical News, J. A. M. A. **112**:755 (Feb. 25) 1939.

20. The Outlook for Diabetes in the 1940's, Statist. Bull. Metrop. Life Ins. Co. **21**:5-8 (May) 1940.

Hereditary Factors.—Identical twins have long been a source of interest in studying the hereditary factor in diabetes. Fischer [21] reported the cases of identical twins, now 8½ years of age. Diabetes developed in 1 at 4 years of age; the other twin is entirely normal and has a normal sugar tolerance curve. It will be interesting to have a further report on these twins. The genetic aspect of diabetes mellitus in Germany [22] was studied in an unselected group of twins. There were 411 pairs of twins among 85,000 diabetic patients. Of these 411 pairs, 46 were enzygotic and 87 were dizygotic. As a result of the study, the conclusion was drawn that diabetes mellitus is purely hereditary.

Traumatic Factors.—In an editorial [23] in which the causal relation of trauma to diabetes was discussed and the literature was reviewed, the general conclusion was drawn that there is no evidence of trauma itself causing diabetes but that it may cause latent diabetes to be manifest.

Diagnosis.—The diagnosis of diabetes mellitus by sugar tolerance curves is necessary in many instances. Matthews, Magath and Berkson [24] made a study of the one hour–two dose dextrose tolerance test (Exton-Rose procedure). As a result of this study, they concluded that the final one hour blood sugar reading is far more significant than any curves which may be drawn. They found that 95 per cent of diabetic patients had a blood sugar reading of 158 mg. or more per hundred cubic centimeters at the end of an hour. They felt that whenever the value for blood sugar was 180 mg. at the end of an hour, a diagnosis of diabetes mellitus should be regarded as certain; if the value was 154 mg. or less, the diagnosis of diabetes should not be made. Tunbridge and Allibone [25] discussed the intravenous dextrose tolerance test, which they preferred to the usual test in which the dextrose is administered orally. Robinson and Shelton [26] reported a variation in sugar tolerance curves in cases of nervous and mental disease and called attention to the fact that conditions other than diabetes mellitus may affect the sugar tolerance curve.

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21. Fischer, A. E.: Diabetes Mellitus in One of Identical Twins, Am. J. Dis. Child. **59**:386-393 (Feb.) 1940.

22. The Genetic Aspect of Diabetes Mellitus, Foreign Letters (Berlin), J. A. M. A. **112**:1091 (March 18) 1939.

23. Trauma and Diabetes, editorial, J. A. M. A. **112**:1592-1594 (April 22) 1939.

24. Matthews, M. W.; Magath, T. B., and Berkson, J.: The One Hour-Two Dose Dextrose Tolerance Test (Exton-Rose Procedure): Diagnostic Significance, J. A. M. A. **113**:1531-1537 (Oct. 21) 1939.

25. Tunbridge, R. E., and Allibone, E. C.: The Intravenous Dextrose Tolerance Test, Quart. J. Med. **9**:11-35 (Jan.) 1940.

26. Robinson, G. W., Jr., and Shelton, P.: Incidence and Interpretation of Diabetic-Like Dextrose Tolerance Curves in Nervous and Mental Patients: A Study of Sixty-Nine Successive Admissions; Preliminary Report, J. A. M. A. **114**:2279-2284 (June 8) 1940.

Fabrykant and Wiener [27] expressed the belief that examination of the urine for three days after the dextrose tolerance test is performed is even more useful than the test itself in determining actual tolerance to carbohydrate.

Wheelon [28] described the paradoxic response of blood sugar of 40 patients to ingested dextrose; the blood sugar level of 20 was 70 mg. or less per hundred cubic centimeters during the course of the dextrose tolerance test. Conn [29] emphasized the necessity of a standard preparatory diet with an adequate intake of carbohydrate before performance of a dextrose tolerance test, for if the intake has been restricted a false positive curve may be obtained. This observation has been noted repeatedly among patients who have been undernourished or who have undergone surgical operations. Conn's statements were most timely. As a matter of fact, a sugar tolerance curve which is not definitely positive should be regarded with suspicion, and the test should be repeated and the result revaluated at a later date. Extreme caution should be exercised in interpretation of the sugar tolerance curve of patients suspected of having hypoglycemia, because, as has been mentioned, there are many patients whose concentration of blood sugar drops to less than normal when this test is performed. The use of the sugar tolerance curve in the diagnosis of hypoglycemia was discussed by Conn.[30]

Associated Pregnancy.—In 1939, Smith and Smith [31] reported their observations on 173 pregnant women. They expressed the opinion that the eclamptic toxemias are characterized by an excessive amount of gonadotropin in the serum and that its occurrence precedes the clinical signs of toxemia by approximately four to six weeks. This change failed to appear in about 12 per cent of the women studied. The increase of gonadotropin in the serum was not present in cases of nephritic or hypertensive toxemia. They suggested that premature delivery is sometimes associated with such excess. The findings in the group of pregnant diabetic women studied followed the same pattern. The authors were inclined to explain the phenomenon as due to failure of the

27. Fabrykant, M., and Wiener, H. J.: The Effect of Added Carbohydrate upon Stabilized Insulin-Treated Diabetics, Am. J. M. Sc. **199**:834-840 (June) 1940.

28. Wheelon, H.: Reverse or "Paradoxical" Blood Sugar Response to Ingested Glucose: A Correlation of Laboratory and Clinical Findings on Forty Patients, Endocrinology **26**:743-752 (May) 1940.

29. Conn, J. W.: Interpretation of the Glucose Tolerance Test: The Necessity of a Standard Preparatory Diet, Am. J. M. Sc. **199**:555-564 (April) 1940.

30. Conn, J. W.: The Spontaneous Hypoglycemia: Importance of Etiology in Determining Treatment, J. A. M. A. **115**:1669-1675 (Nov. 16) 1940.

31. Smith, G. Van S., and Smith, O. W.: The Anterior Pituitary-Like Hormone in Late Pregnancy Toxemia: A Summary of Results Since 1932, Am. J. Obst. & Gynec. **38**:618-624 (Oct.) 1939.

body to use the gonadotropin in the production of increased amounts of the estrogen and progestin steroids, which are normally characteristic of pregnancy.

White and her associates [32] at the Baker Clinic had a most unusual opportunity to study pregnancy in diabetic women. They called attention to the fact that, unlike other complicating diabetic situations, the continued use of insulin did not solve the problem of pregnancy in diabetes. Until recently, it has been nearly as true of the insulin era as of the period before that only every other pregnancy in a diabetic woman terminated successfully. Accidents of such pregnancies do not concern the welfare of the mother, for the maternal mortality rate is low, but they do concern the welfare of the child and result in (1) early spontaneous abortion, miscarriage or premature birth, (2) stillbirth or (3) a neonatal type of death common within twenty-four hours after delivery. They [32b] studied 353 instances of pregnancy among 242 diabetic women encountered since 1898; they included patients whom they treated during pregnancy and those treated elsewhere during that period and seen by them at a later date. Excessive fetal mortality rates have been reported by them and by all other investigators. Excluding those cases in which pregnancy was interrupted by cesarean section, the fetal mortality rate before insulin was introduced was 44 per cent and that after the introduction of insulin 38 per cent. Before the use of insulin, the early and late fetal deaths occurred with equal frequency. Since insulin has been used, 60 per cent of the deaths were late and were due to stillbirth or to a neonatal accident and 40 per cent were attributable to spontaneous abortion. It is much easier to study the problems of late pregnancy than those of early pregnancy because most women come for examination late.

Although for years these neonatal accidents have been attributed to diabetes itself, its complications or its treatment, the authors expressed the opinion that there is now evidence to suggest that these accidents are not due to faulty treatment or to poor control of the diabetes. They noted that even severe coma or hypoglycemia was not incompatible with the life of the child and that these accidents often occurred among the patients under good control, while the pregnancies of some careless patients terminated successfully. Hence, the authors suggested that some "extradiabetic" factor must be sought in order to explain these deaths.

The first suggestion that pregnant diabetic patients may have a hormonal imbalance was made in 1933 by Murphy,[33] who found that

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32. (*a*) White, P., and Hunt, H.: Prediction and Prevention of Pregnancy Accidents in Diabetes, J. A. M. A. **115**:2039-2040 (Dec. 14) 1940. (*b*) White, P.; Titus, R. S.; Joslin, E. P., and Hunt, H.: Prediction and Prevention of Late Pregnancy Accidents in Diabetes, Am. J. M. Sc. **198**:482-492 (Oct.) 1939.

33. Murphy, D. P.: The Excretion of Ovary Stimulating Hormone in the Urine During Pregnancy, Surg., Gynec. & Obst. **56**:914-917 (May) 1933.

excessive amounts of gonadotropin were excreted in the urine of 2 pregnant diabetic women. Smith and Smith [34] found a high incidence of preeclamptic toxemia among diabetic patients. White and her associates, therefore, expressed the opinion that stillbirth and other accidents of this type in their patients were more likely to be related to an abnormal hormonal picture than to any of the other factors described previously. They found that among many diabetic patients the course of pregnancy was uneventful until the sixth month and that thereafter edema, albuminuria and high blood pressure often developed. Shortly after the rise in blood pressure, the fetus died and signs of toxemia disappeared promptly. The entire clinical picture can appear and clear up within a week, but its onset is preceded by an increase in the gonadotropin in the serum [32b] over a period of four to six weeks. Between January 1936 and June 12, 1940, they studied 61 pregnant diabetic women and made several determinations of this principle in the serum throughout the term of each pregnancy. The studies were begun about the twenty-fourth week of pregnancy, and determinations were performed at intervals of five to seven days. Most of the patients had moderately severe to severe diabetes, but all were under adequate dietary and insulin control. In this group, coma developed in only 1 case and severe hypoglycemic shock in only 1. In neither instance was there any interference with the pregnancy. Twenty-five of the 61 patients had normal amounts of gonadotropin in the serum (less than 200 rat units per hundred cubic centimeters). All 25 had an uneventful pregnancy, without toxemia. No premature deliveries and no miscarriages occurred, and there were only 2 infant deaths, a survival rate of 92 per cent. One infant died of asphyxia pallida two hours post partum; necropsy revealed nothing of importance. The other infant died of hemorrhagic disease of the newborn several days post partum. Twelve of the 61 patients had abnormally high values for gonadotropin in the serum, and this value rose steadily until term. Complications developed among all of these patients during pregnancy. Nine had preeclamptic toxemia, and 3 had premature deliveries. All were placed in the hospital and treated routinely for this type of toxemia as soon as it appeared, but notwithstanding, the toxemia progressed. Three fetal deaths occurred within the uterus during the toxemic phase of the pregnancy, and 3 infant deaths occurred after premature delivery.

One diabetic patient had two successive pregnancies, associated with preeclamptic toxemia. The abnormally high values for gonadotropin in

34. Smith, G. Van S., and Smith, O. W.: Further Quantitative Determinations of Prolan and Estrin in Pregnancy, with Especial Reference to Late Toxemia and Eclampsia, Surg., Gynec. & Obst. **61**:27-35 (July) 1935; footnote 31.

the serum fell steadily during the last trimester. As the amount of this substance in the serum decreased, the toxic symptoms were reduced markedly in the first pregnancy and cleared up entirely in the second pregnancy; the symptoms were less severe in the second pregnancy. The decrease in the gonad-stimulating factor was preceded by an increase in estrogen.

Twenty-four of the patients in whose serum the amount of gonadotropin was abnormally high were given replacement therapy. Thirteen received this treatment in the form of estrogenic substance, 150,000 to 300,000 international units of estradiol benzoate (progynon B) given each day, as well as progestin in doses of 10 to 20 mg. Eleven of them received medication in the form of stilbestrol in doses of 40 to 120 mg. daily and pregnolinine in doses of 10 to 40 mg. daily. The progestin was administered because it had been demonstrated that the excretion of sodium pregnandiol glucuronidate had been lowered. In some instances, testosterone was substituted for the progestin. Although most of these patients had symptoms of preeclamptic toxemia associated with the elevated values for gonadotropin in the serum, including albuminuria, edema, hypertension, headache, nausea and vomiting, the treatment with estrogen or androgen was followed by a drop in the gonadotropin in the serum. Progressive toxemia and miscarriages did not occur; signs of improvement in the general condition, including lessening of the toxic symtoms, were noted. Only 1 fetal and 1 infant death occurred in this series. In the first case, in which the replacement therapy had been stopped because of the high cost of the estrogen, toxemia recurred and stillbirth resulted. In the other instance the infant died of erythroblastosis a day or so after birth.

It is of interest to note that even with administration of such massive doses of stilbestrol no side reactions and no demonstrable decrease in liver function were noted.

White and her associates [32b] also studied the question of hypoglycemia of the infants of diabetic mothers. This subject has been reviewed by Randall and Rynearson.[35] White and her co-workers stated that in their series of patients hypoglycemia developed but did not result in death of the infant. Only 10 of 127 blood sugar values were found to be within the hypoglycemic range. She and her co-workers expressed the opinion also that the large size of the baby was not related to the hyperglycemia [32b] of the mother, but rather that it might be due to an imbalance of hormones. These papers have been reviewed in such detail because of their importance and because of the hope that others

35. Randall, L. M., and Rynearson, E. H.: Delivery and Care of the New-Born Infant of the Diabetic Mother, J. A. M. A. **107**:919-924 (Sept. 19) 1936.

interested in this field will perform similar studies on similar patients. The facilities necessary for such a study and the high cost of the treatment as outlined by these authors may make this method difficult for many to attempt.

Helwig [36] studied the pancreases of 9 infants of diabetic mothers and 9 infants of nondiabetic mothers. The islands of Langerhans of the infants of diabetic mothers exhibited a variable degree of hyperplasia and hypertrophy. The authors concluded that "some infants of diabetic mothers have definitely larger amounts of insular tissue than infants of nondiabetic mothers." They reported but little correlation between the concentration of sugar in the infant's blood and the size of the islands of Langerhans. Miller and Ross [37] studied the relation of hypoglycemia to the symptoms observed among infants of diabetic mothers. The average value for blood sugar of 6 infants born to diabetic mothers was 29.7 mg. per hundred cubic centimeters, as compared with 31.8 mg. for 20 premature infants born to normal mothers and with 49.9 mg. for 17 full term infants born to normal mothers. The authors expressed the belief that there was no relation between the level of the blood sugar and an infant's symptoms and that the symptoms and the clinical course could in each instance be explained better on the basis of organic disease. Ketteringham [38] studied results of dextrose tolerance tests performed on newborn infants both of nomal and of diabetic mothers. He found that infants and young adults responded to the tests in the same way. The tests were much more difficult to perform on the infants of diabetic mothers, and the results were less satisfactory, owing to technical factors.

Rosenthal [39] reviewed the entire subject of children born to diabetic mothers. He discussed the high mortality rate and the possible contributory factors, including gigantism, the higher incidence of congenital defects and hypoglycemia. He stated that it is important to undertake measures to prevent some of these unfortunate occurrences and suggested following one of three lines or a combination thereof: (1) adequate control of the mother's diabetes, (2) treatment with estrogen, as suggested by White, and (3) cesarean section in the thirty-sixth or thirty-seventh week, as suggested by Randall and one of us (E. H. R.).

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36. Helwig, E. B.: Hypertrophy and Hyperplasia of Islands of Langerhans in Infants Born of Diabetic Mothers, Arch. Int. Med. **65**:221-239 (Feb.) 1940.

37. Miller, H. C., and Ross, R. A.: Relation of Hyperglycemia to the Symptoms Observed in Infants of Diabetic Mothers: Report of Six Cases, J. Pediat. **16**: 473-481 (April) 1940.

38. Ketteringham, R. C.: Dextrose Tolerance Tests of the Newborn, Am. J. Dis. Child. **59**:542-553 (March) 1940.

39. Rosenthal, R.: Children of Diabetic Mothers, editorial, Minnesota Med. **23**: 259-262 (April) 1940.

Juvenile Diabetes.—Barach,[40] Grishaw, West and Smith,[41] and White [42] discussed some of the problems of juvenile diabetes. Their articles are fairly typical of those which are being written on this subject, and only two comments need to be made: First, more and more diabetic children are leading perfectly normal lives and are developing in a perfectly normal fashion. This is due as much as anything to the fact that these children are more frequently given normal diets adequate in caloric, mineral and vitamin content. Diabetic dwarfism was seen much more frequently when diets low in content of calories and vitamins were prescribed. Diabetic children now are growing normally and should become useful citizens. The other comment is that many articles are being written suggesting that these diabetic children have an endocrine imbalance. Personally, we feel that there are too many unwarranted conclusions about this condition with not enough good evidence. Too many of these children are receiving injections of endocrine preparations of one type or another or, what is much worse, are being given them by mouth. While it is true that diabetic children may have a disturbance of some of the other endocrine glands, the only real facts available indicate that the only acknowledged deficiency is a deficiency of insulin and that many of these other changes are secondary to the disease rather than contributing factors to the production of the condition. No one has presented any convincing evidence that there is better treatment for the diabetic child than the accepted standardized procedure of an adequate diet and sufficient insulin for the control of the disease.

Pancreas and Organs of Secretion.—Among adults there has been a little better opportunity for studying the possible relation of the pancreas to other organs of internal secretion. Gessler and his associates [43] studied 5 diabetic women who had passed the menopause and who were treated with intramuscular injections of estradiol benzoate. Three of the 5 patients improved with estrogenic therapy. Spiegelman [44] reported also on the influence of estrogen on the insulin requirements of diabetic patients. He studied 9 diabetic patients for four months before estro-

40. Barach, J. H.: Growth in Diabetic Children, Pennsylvania M. J. **42**:1459-1467 (Sept.) 1939.

41. Grishaw, W. H.; West, H. F., and Smith, B.: Juvenile Diabetes Mellitus, Arch. Int. Med. **64**:787-799 (Oct.) 1939.

42. White, P.: Endocrine Manifestations in Juvenile Diabetes, Arch. Int. Med. **63**:39-53 (Jan.) 1939.

43. Gessler, C. J.; Halsted, J. A., and Stetson, R. P.: Effect of Estrogenic Substance on the Blood Sugar of Female Diabetics After the Menopause, J. Clin. Investigation **18**:715-722 (Nov.) 1939.

44. Spiegelman, A. R.: Influence of Estrogen on the Insulin Requirement of the Diabetic, Proc. Soc. Exper. Biol. & Med. **43**:307-308 (Feb.) 1940.

genic therapy was begun, for five months during its administration and for three months after its administration had been discontinued. He reported a variable decrease in the insulin requirements of the diabetic patients treated. It is interesting to note that the age of the patient was important. Surprisingly, among the premenopausal patients there was a daily saving of insulin of 63 per cent. Of the postmenopausal patients, there was a daily average saving of only 41 per cent. The authors did not state whether the decreased expense from the standpoint of the amount of insulin used was more than overbalanced by the increased expenditure for the estrogenic product. Cantilo [45] reported the results of his studies on 40 diabetic women who were at the menopausal or postmenopausal age. All patients treated were reported to have improved. Recently Mazer and his associates [46] reported 4 cases of diabetes in which stilbestrol was given for the treatment of menopausal symptoms. When 1 mg. of stilbestrol (equivalent to 50,000 international units of estrogen) was given hypodermically twice weekly, the insulin requirement was decreased materially, although the diet was not altered. The authors concluded, "There is, nevertheless, no advantage in the use of the estrogens, natural or synthetic, in the treatment of diabetes mellitus unless a severe menopausal syndrome coexists."

Observations such as those just mentioned are interesting but are far from conclusive. Such studies should be continued, but unwarranted conclusions should be avoided.

Acromegaly and Diabetes.—Coggeshall and Root [47] studied the coexistence of acromegaly and diabetes mellitus and analyzed 29 cases in which these two conditions were associated. The onset of acromegaly preceded that of diabetes mellitus by an average of nine and two-tenths years. They also reported a predisposition to diabetes in the families of diabetic patients who have acromegaly as compared with the families of patients who have acromegaly only. All these and similar clinical observations bear testimony to the interrelation of the glands of internal secretion, particularly with regard to the pituitary gland. We do not believe that knowledge at present has crystallized to the point where some of these comments may be accepted as facts; for example, we cannot agree with the observations and conclusions made by Hutton

45. Cantilo, E.: Successful Responses in Diabetes Mellitus of the Menopause Produced by the Antagonistic Action of the Hormones Toward Pituitary Activity, Endocrinology **26**:917-918 (May) 1940.

46. Mazer, C.; Israel, S. L., and Ravetz, E.: The Synthetic Estrogen, Stilbestrol: An Experimental and Clinical Evaluation, J. A. M. A. **116**:675-681 (Feb. 22) 1941.

47. Coggeshall, C., and Root, H. F.: Acromegaly and Diabetes Mellitus, Endocrinology **26**:1-25 (Jan.) 1940.

and his associates.[48] They stated that in many cases essential hypertension and diabetes mellitus resemble each other in so many respects as to suggest common etiologic factors, and they incriminated the pituitary, adrenal and thyroid glands. They reported the results of roentgen therapy over the adrenal and over the pituitary glands. We regard the evidence presented in this article as unconvincing and inconclusive.

Pancreatic Lesions and Diabetes.—Pancreatic lithiasis and diabetes still are reported as coexistent. Labbé [49] published an excellent review of this topic in 1938. Rockwern and Snively [50] reviewed the literature and reported the findings in 125 cases. Moolten [51] reported a case of pancreatic lithiasis associated with diabetes and extensive necrotic pneumonia of mixed bacterial type.

Another condition of the pancreas with which diabetes occasionally coexists is acute pancreatitis. The association of these two diseases was reviewed recently by Shumacker.[52] It is not surprising that diabetes develops among patients who have this acute pancreatic lesion, but it seems strange that it does not develop with greater frequency. Shumacker found that diabetes occurred in only 2 per cent of patients with severe pancreatitis and that of those patients who survived the acute illness, diabetes developed in 3 to 10 per cent.

Diabetes and Diabetes Insipidus.—Talbott and associates [53] reported another case of diabetes insipidus associated with diabetes mellitus.

Miscellaneous Acute Complications and Diabetic Coma.—Duncan and Jewesbury [54] discussed the management of acute complications of diabetes mellitus. They discussed the treatment of infection, degenerative change, gangrene, coronary occlusion, surgical conditions, ketosis and

48. Hutton, J. H.; Case, J. T.; Culpepper, W. L.; Olson, E. C., and Madden, E. E.: The Endocrine Aspect of Essential Hypertension and Diabetes Mellitus, Endocrinology **26**:418-426 (March) 1940.

49. Labbé, M.: Lithiase pancréatique et diabète, Arch. d. mal. de l'app. digestif **28**:913-934 (Nov.) 1938.

50. Rockwern, S. S., and Snively, D.: Pancreatic Lithiasis Associated with Pancreatic Insufficiency and Diabetes Mellitus: Report of Two Cases, Arch. Int. Med. **65**:873-881 (May) 1940.

51. Moolten, S. E.: Pulmonary Infection and Necrosis in Diabetes Mellitus: Report of a Case of Dissecting Necrotic Pneumonia Complicating Pancreatic Lithiasis, Arch. Int. Med. **66**:561-578 (Sept.) 1940.

52. Shumacker, H. B.: Acute Pancreatitis and Diabetes, Ann. Surg. **112**:177-200 (Aug.) 1940.

53. Talbott, J. H.; Coombs, F. S.; Consolazio, W. V., and Pecora, L. J.: Diabetes Insipidus Associated with Diabetes Mellitus: Metabolic Studies and Report of a Case, Arch. Int. Med. **66**:607-624 (Sept.) 1940.

54. Duncan, G. G., and Jewesbury, E. C. O.: The Management of the Acute Complications of Diabetes Mellitus, M. Clin. North America **23**:1533-1559 (Nov.) 1939.

pregnancy. In cases of mild infection they advised the administration of unmodified insulin if the level of fasting blood sugar exceeded 120 mg. per hundred cubic centimeters or if after meals the blood sugar exceeded 160 mg. In cases of moderately severe infection, they divided the usual dose of insulin into four equal doses. A specimen of the urine was examined before the administration of insulin; the patient was given a fourth of the total amount of food after the insulin had been administered. The amounts of insulin given were regulated by the results of urinalysis performed before administration. In cases of severe infection the authors advised that the total food and insulin be given in six equal doses. If the patient improved, the daily feedings were reduced to four and then to three, as before infection occurred. They felt that it was preferable to decrease the amount of insulin per dose rather than to omit a dose. They also commented that if infection of the urinary tract was present the dextrose in the urine may have been reduced by the organisms present, and the resultant absence or decrease may be misleading. In a discussion of surgical complications, the authors commented on their belief that a high content of blood fats predisposes to arteriosclerotic changes and gangrene, which concept had led them to reduce the amount of fat in the diet. In the discussion of gangrene, they gave as their indications for surgical intervention a rapid spreading of the gangrene, osteomyelitis, severe pain or advanced vascular disease. In regard to surgical operation, they advised the delay of anything except emergency intervention until the diabetes was under complete control. They agreed that spinal or local anesthesia, as well as that induced by nitrogen monoxide, is suitable, but they advised against the use of chloroform or ethyl chloride.

The treatment of diabetic coma employed by Duncan and Jewesbury is energetic. They advised the immediate administration of 100 units of protamine zinc insulin and 100 units of regular insulin subcutaneously and thereafter regular insulin every half-hour until the coma was controlled completely. They also utilized physiologic solution of sodium chloride and advised the use of sodium bicarbonate when the occasion demanded. Himsworth [55] again called attention to the fact that in cases of diabetic acidosis the abdominal symptoms may be sufficiently severe to suggest the presence of an intra-abdominal pathologic condition. He advised delay of operation until the ketosis was controlled. Duff and Williams [56] discussed the question of diabetes in operations on the urinary tract. Of 3,158 cases of disease of the urinary tract observed

55. Himsworth, H. P., in Discussion on Surgery in Diabetic Patients, Proc. Roy. Soc. Med. **32**:1002-1008, 1939.

56. Duff, J., and Williams, F. W.: Diabetes in Surgical Urology, J. Urol. **40**: 446-451 (Sept.) 1938.

over a period of five years, diabetes was present in 39; in 17 of them the patients were operated on, and the authors commented that with proper preoperative treatment they had found no greater operative risk than that in a comparable group of nondiabetic patients.

Diabetic Coma.—Owens and Rockwern [57] presented their observations in regard to the prognosis in cases of diabetic coma. They made the rather startling claim that the carbon dioxide level of the blood is not of prognostic importance. They felt, rather, that a more important basis for determining the eventual outcome is the patient's mental state. They feel that the mortality in coma depends primarily on the extent and previous duration of brain damage which is present when therapy is begun. The damage to the central nervous system seems to them unrelated to the severity of coexisting acidosis and pursues a course as yet unexplained.

Heck and Hall [58] remarked on the leukemoid reactions of the myeloid type which may be seen in cases of diabetic coma. The blood picture is similar to, or indistinguishable from, that seen in cases of leukemia. It is commonly associated with leukocytosis and a leukemoid reaction. Myeloid immaturity disappears promptly after institution of measures for the control of diabetes.

Vascular Disease.—Pearl and Kandel [59] studied the peripheral vascular system of 100 unselected diabetic patients. More than half of the patients complained of vascular symptoms; the majority of them disclosed abnormalities of the peripheral pulsation and other signs of peripheral vascular derangement. About 50 per cent of them had generalized arteriosclerosis. No relation was found between the degree of arteriosclerosis and the duration of the diabetes, but a direct relation was reported between the severity of the symptoms and the degree of peripheral vascular disease. Bowen, Regan and Koenig [60] offered proof that arteriosclerosis of the lower extremities can be prevented or delayed by continuous control of the diabetes, provided control is instituted early enough after inception of the diabetes. Root and his associates [61]

57. Owens, L. B., and Rockwern, S. S.: Prognosis in Diabetic Coma: Basic Importance of Mental State, Am. J. M. Sc. **198**:252-260 (Aug.) 1939.

58. Heck, F. J., and Hall, B. E.: Leukemoid Reactions of the Myeloid Type, J. A. M. A. **112**:95-101 (Jan. 14) 1939.

59. Pearl, F. L., and Kandel, A.: Peripheral Vascular Status of One Hundred Unselected Patients with Diabetes, Arch. Surg. **39**:86-96 (July) 1939.

60. Bowen, B. D.; Regan, J. S., and Koenig, E. C.: The Development of Arteriosclerosis in the Diabetic, Based on the Study of a Group of Patients During Ten to Thirteen Years, Ann. Int. Med. **12**:1996-2005 (June) 1939.

61. Root, H. F.; Bland, E. F.; Gordon, W. H., and White, P. D.: Coronary Atherosclerosis in Diabetes Mellitus: A Postmortem Study, J. A. M. A. **113**:27-30 (July 1) 1939.

studied the question of coronary atherosclerosis associated with diabetes mellitus. The study was made post mortem and consisted in a comparison of atherosclerotic lesions in the coronary arteries of 349 diabetic patients and 3,400 nondiabetic patients. They found that the incidence of coronary occlusion was much more frequent in the diabetic than in the nondiabetic group. For example, of the patients between the ages of 40 and 60, 23 per cent of those who had diabetes had coronary occlusion, as compared with 6 per cent of the nondiabetic group. Coronary sclerosis without occlusion also was found more commonly in the diabetic group. There was no significant atherosclerosis with occlusion or narrowing in 49 per cent of the diabetic group or in 82 per cent of the nondiabetic group. They found that occlusion of a coronary artery occurred among diabetic women almost as frequently as among diabetic men, whereas in the nondiabetic patients under 60 years of age it was far less frequent among women than among men.

Williams and O'Kane [62] suggested a clinical classification of lesions of the lower extremities associated with diabetes. They separated vascular involvement from infectious involvement. Murray [63] also discussed the question of diabetic infection and gangrene. He suggested that increasing attention should be given to minor infectious lesions. He also advised local amputation in a few cases of localized gangrene, but emphasized that radical amputation is required in cases of fulminating infection or extensive gangrene.

Diabetes and Ocular Conditions and Neuritis.—Smith [64] listed the diabetic manifestations seen in cases of ophthalmic disease. He commented on the rarity of lipaemia retinalis and pointed out that Moore of London reported he had not seen a case of this condition since insulin was introduced. Retrobulbar neuritis occasionally is seen among older persons. It produces a typical small central scotoma and usually responds to treatment. This condition, if allowed to progress, may result in atrophy. He felt that iritis may be due to lowered resistance to infection. The cataracts are mostly of the senile type, which develop earlier among diabetic patients than among nondiabetic patients. A true diabetic cataract in a young person occurs bilaterally and develops rapidly.

Smith found, too, that diabetic retinitis usually is associated with hypertension, vascular disease and albuminuria. It may be difficult

62. Williams, F. W., and O'Kane, T. J.: Clinical Classification of Lesions of the Lower Extremities Associated with Diabetes: A Guide for Operation and the Level of Amputation, Arch. Surg. **40**:685-693 (April) 1940.

63. Murray, G.: Diabetic Infection and Gangrene, Canad. M. A. J. **41**:246-250 (Sept.) 1939.

64. Smith, W. J.: Diabetic Manifestations in Ophthalmology, Southwestern Med. **23**:14-15 (Jan.) 1939.

to decide the cause of retinitis. He stated that hemorrhage at the time of operation on the eye occurs more frequently among diabetic than among nondiabetic patients. Refractive errors are common. Some undoubtedly are due to an alteration of osmotic pressure in the aqueous humor with altered index of refraction in the lens cortex. This change is commonly seen shortly after treatment with insulin is instituted. Recent literature does not disclose anything hopeful in the treatment of diabetic retinitis. The so-called antihemorrhagic vitamins, such as vitamins C and K, are being given a trial and snake venom is also being used because of its antihemorrhagic effect. It is to be hoped that within a few years the effect of the latter agent may be evaluated properly. Another discouraging complication of diabetes is diabetic neuritis. Wohl [65] stated that diabetic neuritis is associated with a lack of vitamin B.

Vitamin Deficiency and Metabolism of Carbohydrate.—Sydenstricker and his associates [66] reported 2 cases in which complications of diabetes occurred; clinical signs of pellagra developed when the carbohydrate content of the diet was increased and an increased amount of insulin was given. In both cases the patients responded to vitamin therapy. The authors expressed the opinion that the rapid metabolism of carbohydrates secured among diabetic patients treated with insulin is accompanied by the correspondingly rapid depletion of the coenzymes; in this way signs of avitaminosis may be produced. Other explanations, such as inadequate absorption or storage of vitamins and coenzymes, were considered. Rudy [67] also reported a case in which diabetes was associated with a vitamin deficiency disease.

Owens and his associates [68] evaluated vitamin B therapy for diabetic patients. They expressed the opinion that the usual diabetic diets contain adequate amounts of thiamine and riboflavin in relation to their total caloric value. They did not find that the administration of large amounts of thiamine hydrochloride and riboflavin for many weeks to patients with well controlled diabetes had any effect on the requirement of insulin or that it altered the severity of the diabetes. They concluded that diabetic patients did not need vitamin therapy when the diabetes was well controlled. They did feel, however, that thiamine hydrochloride

65. Wohl, M. G.: Neuritis of Diabetes Mellitus and Avitaminosis B, J. A. M. A. **113**:164 (July 8) 1939.

66. Sydenstricker, V. P.; Geeslin, L. E., and Weaver, J. W.: Avitaminosis Occurring in Diabetic Patients Under Insulin Therapy, J. A. M. A. **113**:2137-2138 (Dec. 9) 1939.

67. Rudy, A.: An Unusual Case of Deficiency Disease in a Patient with Diabetes Mellitus, Endocrinology **27**:206-211 (Aug.) 1940.

68. Owens, L. B.; Rockwern, S. S., and Brown, E. G.: Evaluation of Vitamin B Therapy for Diabetes, Arch. Int. Med. **66**:679-687 (Sept.) 1940.

has a beneficial effect on patients suffering from diabetic neuritis. Kaufman [69] reviewed the influence of thiamine on the level of blood sugar in diabetic patients. He found absolutely no effect from the use of this vitamin in the treatment of patients with uncomplicated diabetes. Brazer and Curtis [70] discussed vitamin A deficiency in diabetes mellitus. They studied a group of 20 patients who had juvenile diabetes; all were found to have poor adaptation to light. Three of the group were subjectively aware of night blindness, and 9 of them disclosed cutaneous changes compatible with deficiency of vitamin A. The daily administration of 60,000 units of crystalline carotene dissolved in vegetable oil for as long as fourteen days did not affect the adaptation to light of patients who had diabetes mellitus. However, when 60,000 units of vitamin A were administered daily to patients in the form of concentrated fish liver oils, their adaptation to light returned to normal or near normal in periods ranging from three to twenty-one days. The authors expressed the belief that the cause of poor adaptation to light in cases of juvenile diabetes appeared to be due to an inability to convert carotene into vitamin A.

Dye and Chidsey [71] studied the utilization ratio for ketone bodies and total carbohydrate and its relation to the problem of ketosis. They used 9 normal, 7 eviscerated and 10 depancreatized dogs. In addition to studying the problem of ketosis, they also confirmed the observations of Soskin and Levine that the consumption of carbohydrate by a diabetic dog at its characteristic blood sugar level may be as high or even higher than that of a normal animal at its characteristic blood sugar level. They concluded that by the exclusion of an extrahepatic origin of ketosis and seat of "antiketosis" the present evidence supported the "overproduction" theory. According to this theory, the primary, if not the only, site of production of ketone bodies is the liver, and the antiketogenic action of insulin, dextrose and other glycogen formers is one of inhibiting the production of these bodies by this organ, possibly through a mechanism which involves the anterior lobe of the pituitary gland.

Diet.—Limited space prevents detailed consideration of the various types of diet now used in the treatment of diabetes mellitus. Suffice it to say that there is as yet no conclusive evidence that any one type of diet is suitable for every physician to prescribe. Some continue to

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69. Kaufman, R. E.: Influence of Thiamine on Blood Sugar Levels in Diabetic Patients, Arch. Int. Med. **66**:1079-1086 (Nov.) 1940.

70. Brazer, J. G., and Curtis, A. C.: Vitamin A Deficiency in Diabetes Mellitus, Arch. Int. Med. **65**:90-105 (Jan.) 1940.

71. Dye, J. A., and Chidsey, J. L.: Ketone Body-Total Carbohydrate Utilization Ratios and Their Relation to the Problem of Ketosis, Am. J. Physiol. **127**: 745-750 (Nov.) 1939.

believe that the diet should be high in carbohydrate and low in fat; this opinion is based on the incidence of arteriosclerosis in cases of diabetes mellitus. The evidence for this statement is as yet not approved generally. It can be said that the majority of internists interested in the treatment of diabetes mellitus now are prescribing diets which are higher in carbohydrate and lower in fat than those which were used previously.

Richardson [72] presented a simplified method for calculation of diabetic diets and listed seven diets in order to simplify the figuring. In these diets, all portions were given, with the exception of the amount of butter and bread necessary to make up the caloric needs. The physician need only know the amount of protein desired in order to find a suitable diet for a patient. This method is similar to that which has been employed for many years at the Mayo Clinic. Lovell and Rabinowitch [73] discussed the factors influencing the storage of protein with low caloric diets. Studies were made of the nitrogen metabolism of diabetic patients treated with various low caloric diets which contained different amounts of carbohydrate and fat and different amounts of vegetable and animal protein. They expressed the opinion that the carbohydrate tends to enhance, whereas the fat tends to interfere with, the storage of protein in the body. The latter is influenced not only by the total amount of protein in the diet but by the relative amount of protein of high biologic (protein-sparing) value.

INSULIN

Mainzer [74] studied the hypersensitivity to insulin of patients who have pellagra. He commented on some of the points which pellagra and Addison's disease have in common and noted that anatomic lesions of the adrenal cortex may be found in many cases of pellagra. The author studied the blood sugar curve in 16 of 21 cases of pellagra after subcutaneous injection of 5 units of unmodified insulin. He found that the resultant decreased values for blood sugar were marked and persisted for more than five hours. The subsequent elevation of the level of blood sugar was retarded or absent. In several cases this small dose of insulin produced severe hypoglycemic shock. The abnormal reaction persisted even after clinical improvement or cure of the pellagra, and consequently the author suggested that it was not due to a deficiency of the vitamin B complex. Mainzer expressed the belief that neither the liver nor the

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72. Richardson, R.: A Simplified Method for Calculating Diabetic Diets, Am. J. M. Sc. **199**:102-108 (Jan.) 1940.

73. Lovell, M. E., and Rabinowitch, I. M.: Factors Influencing Storage of Protein with Low-Calorie Diets, J. Nutrition **18**:339-351 (Oct.) 1939.

74. Mainzer, F.: Ueber Pellagra: II. Insulin—Ueberempfindlichkeit bei Pellagrakranken, Acta med. Scandinav. **100**:208-243 (June 14) 1939; abstracted, J. A. M. A. **113**:986 (Sept. 2) 1939.

anterior lobe of the pituitary gland could be considered responsible for this exaggerated response to insulin, but that it could be related to a functional failure of the adrenal glands of patients who have pellagra.

Ralli and Sherry [75] studied the effect of insulin on the plasma level and urinary excretion of vitamin C of pancreatectomized dogs. They found that the plasma level and the urinary excretion of vitamin C decreased markedly as soon as a subcutaneous dose of insulin became effective. If dextrose was administered intravenously at the same time that the plasma level and the urinary excretion of vitamin C were observed to be reduced, the effect of the insulin could be overcome and the plasma level of vitamin C returned to normal. Burke and McIntyre [76] studied the effect of nicotinic acid and the vitamin B complex on the tolerance of rats to insulin. Various fractions of the vitamin B complex produced varying results. The authors concluded that nicotinic acid was at least partially responsible for the antagonistic action of the heat-stable portion of the vitamin B complex to the hypoglycemic effect of insulin.

Gemmill [77] studied the effect of insulin on the glycogen content of isolated muscles and measured it by determining the glycogen content of different isolated muscles after they had been suspended for some time in Ringer's solution containing dextrose and with or without the addition of unmodified insulin. The glycogenic content of the sartorius muscles of frogs did not change in the presence of insulin; however, the diaphragmatic muscle of rats disclosed an appreciable increase in glycogen when insulin was present. When the amount of glycogen present in rats' diaphragms which had been suspended in the solution to which insulin had been added was compared with the content of glycogen present prior to that procedure, it was found that a definite synthesis of glycogen had taken place. If the surrounding medium did not contain dextrose, or if ovalbumin or small amounts of inactivated insulin were substituted for the active insulin, the content of glycogen in the muscle did not increase. The insulin did not increase the oxygen uptake of a rat's diaphragm. The author concluded that insulin aids in the conversion of dextrose to glycogen in isolated muscle.

Types of Insulin.—Recently many articles have been written in regard to the best type of insulin for general use, the best time of day for its administration and a number of other related problems. It is

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75. Ralli, E. P., and Sherry, S.: Effect of Insulin on Plasma Level and Excretion of Vitamin C, Proc. Soc. Exper. Biol. & Med. **43**:669-672 (April) 1940.

76. Burke, J. C., and McIntyre, A. R.: Nicotinic Acid and the Vitamin B Complex in Insulin Tolerance, J. Pharmacol. & Exper. Therap. **67**:142-146 (Oct.) 1939.

77. Gemmill, C. L.: The Effect of Insulin on the Glycogen Content of Isolated Muscles, Bull. Johns Hopkins Hosp. **66**:232-244 (April) 1940.

impossible to review all of these articles or to review any of them in detail. A few, however, have been included in one footnote.[78] In summary, it may be said that there is a unanimity of opinion that protamine zinc insulin has a definite role in the treatment of diabetes mellitus. There is not such agreement, however, in regard to the other types of insulin. There is little evidence that crystalline insulin, by whatever name it is known, has a much different effect from the unmodified type of insulin used in past years. By now, each physician has had an opportunity to determine whether he obtains the best results from the administration of protamine zinc insulin in the morning or at night, whether it is better to administer the protamine and the regular insulin in separate syringes and at separate sites or in the same syringe and whether great attention must be paid to the amount of glycosuria or to the level of blood sugar. All these and many other problems will undoubtedly remain controversial for a number of years.

Subcutaneous implantation of tablets of insulin is also being studied. Recent reports do not suggest that this method is yet ready for general clinical application.[79] If it were possible to implant subcutaneously the correct amount of insulin needed to control the diabetes for a long period, treatment of the disease would have made a definite advance. The most obvious disadvantage is that after implantation there is no way in which allowance may be made for any change in the patient's requirement for insulin. Regardless of the amount of his physical activity, the state of his health or the amount of food ingested, the implanted insulin would be absorbed at the same rate.

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78. Martin, H.; Drury, D. R., and Strouse, S.: Basal Insulin Requirement in Diabetes Mellitus, Arch. Int. Med. **66**:78-92 (July) 1940. Mark, M. F.: Optimum Time for Administration of Protamine Zinc Insulin, ibid. **64**:897-906 (Nov.) 1939. Ricketts, H. T., and Wilder, R. M.: Solutions of Amorphous Insulin and Solutions of Zinc Insulin Crystals: Clinical Studies on the Comparative Speed and Duration of Action, J. A. M. A. **113**:1310-1312 (Sept. 30) 1939. Duncan, G. G.; Cuttle, T. D., and Jewesbury, E. C. O.: Observations on the Comparative Clinical Values of Zinc Insulin Crystals in Solution and Unmodified Insulin, Bull. Ayer Clin. Lab., Pennsylvania Hosp. **3**:293-306 (Dec.) 1939. Allen, F. M.: Comparison of Different Preparations of Amorphous and Zinc Crystalline Insulin, Endocrinology **26**:208-217 (Feb.) 1940. Jackson, R. L.; Boyd, J. D., and Smith, T.: Interchangeability of Zinc Crystalline Insulin and Amorphous Insulin, Am. J. Dis. Child. **59**:1050-1053 (May) 1940. Hechter, O.; Levine, R., and Soskin, S.: Possible Physiologic Significance of the Zinc Content of Insulin, Proc. Soc. Exper. Biol. & Med. **43**:361-363 (Feb.) 1940. Morris, N.: The Newer Insulins, Glasgow M. J. **133**:1-19 (Jan.) 1940.

79. Mark, J., and Biskind, G. R.: The Increased Duration of Insulin Action by the Use of Protamine Zinc Insulin in Pellet Form, Endocrinology **26**:444-448 (March) 1940. Parkes, A. S., and Young, F. G.: The Influence of the Subcutaneous Implantation of Tablets of Solid Insulin on the Blood Sugar Level of the Rabbit, J. Endocrinol. **1**:108-116 (June) 1939.

Globin insulin is a combination of insulin and beef globin. Recent reports indicated that it is certainly worthy of further clinical trial.[80] Marks pointed out that this type of insulin is not as soluble in serum as is protamine zinc insulin and that globin does not interact with the serum proteins but simply combines with the insulin. He reported that it has a more rapid effect during the first two or three hours after injection than does protamine zinc insulin. The prolonged hypoglycemic effect thereafter is about equal in intensity to that of protamine zinc insulin, but is shorter in duration, ending within twenty-four hours. Therefore, although it takes care of the meals eaten during the course of the day, it does not necessitate bedtime feedings in order to prevent hypoglycemia during the night.

Many physicians have been hoping for a type of insulin which would require only one injection and which would have not only a prompt effect that would take care of the ingested food but a prolonged stabilizing effect. As will doubtless be recalled, it was at first thought that the ideal type of insulin had at last been discovered in protamine zinc insulin. There are still those, notably Tolstoi and his associates, who prefer to use a single dose of protamine zinc insulin, even though it may not control the glycosuria or the hyperglycemia. In July 1939 they[81] reported their results of the treatment of 2 patients who had severe diabetes and who were given a constant diet, consisting of 200 Gm. of carbohydrate, 75 Gm. of protein and 60 Gm. of fat, and a constant dose of 50 units of protamine zinc insulin every morning before breakfast over a period of strict observation in the metabolic ward. Despite the fact that each patient had constant hyperglycemia and glycosuria, excreting as much as 150 Gm. of dextrose in twenty-four hours, neither had polyuria or polydipsia, neither lost weight and neither showed a change in nitrogen equilibrium during the period of observation. Subsequently, these same authors[82] reported on a series of 84 ambulatory

80. Bauman, L.: Clinical Experience with Globin Insulin, Am. J. M. Sc. **198**: 475-481 (Oct.) 1939. Reiner, L.; Searle, D. S., and Lang, E. H.: On the Hypoglycemic Activity of Globin Insulin, J. Pharmacol. & Exper. Therap. **67**:330-340 (Nov.) 1939. Marks, H. E.: A New Globin Insulin: The Importance of Carbohydrate Distribution in the Control of Diabetes with the Modified Insulins, M. Clin. North America **24**:649-670 (May) 1940. Andrews, G. B.; Groat, W. A.; Wood, A. V., and Jones, M. L.: Globin Insulin: A Clinical Study, New York State J. Med. **40**:913-917 (June 15) 1940.

81. Tolstoi, E., and Weber, F. C.: Protamine Zinc Insulin: A Metabolic Study; Treatment in Two Cases of Severe Diabetes by Equally and Unequally Divided Diets, with Comments on Criteria for Treatment, Arch. Int. Med. **64**:91-104 (July) 1939.

82. Tolstoi, E., and Weber, F. C.: Protamine Zinc Insulin: A Clinical Study; Report of a Group of Diabetic Patients in Whose Cases Glycosuria Was Disregarded for One Year, Arch. Int. Med. **66**:670-678 (Sept.) 1940.

patients similarly treated for a year or more. These patients also were given estimated diets which contained 200 to 250 Gm. of carbohydrate and a single dose of protamine zinc insulin each morning. Twenty-seven patients out of this group had such severe diabetes that glycosuria was present constantly; no effort was made to obtain sugar-free urine by altering the diet or the dose of insulin. However, if ketonuria was present or if the patient lost weight, the amount of protamine zinc insulin was increased until the ketonuria disappeared and a gain in weight was noted. Severe ketonuria was specifically treated by oral administration of sodium chloride plus frequent doses of unmodified insulin. Among these 27 patients, 19 gained weight, 6 lost weight and 2 maintained the same weight; none of them had polyuria or polydipsia; none showed any increased incidence of infection, and all maintained a normal nitrogen balance.

Tolstoi suggested that for patients who are being treated with protamine zinc insulin the therapy may be considered as adequate when there are maintenance of body weight, freedom from symptoms of diabetes and absence of ketonuria. He stated that he "was not concerned about the hyperglycemia or the amount of dextrose excreted."

Much controversy has been aroused by these reports. Joslin and his associates [83] challenged Tolstoi's statement that patients can excrete as much as 150 Gm. of dextrose in twenty-four hours and still maintain their weight and their state of nitrogen equilibrium over a prolonged period. They further pointed out that it is "unlikely" that these patients can remain free of polyuria or polydipsia while they are excreting in the urine 5 to 10 per cent of sugar. They condemned Tolstoi's practice of allowing patients who have definite acidosis to carry out their own treatment at home and stated that forty-two years of experience with diabetes in their own clinic had shown them that methods designed to control hyperglycemia and glycosuria result in a reduced incidence of coma and other complications of diabetes and an increase in the length of life of the average diabetic patient.

Tolstoi [84] shortly thereafter replied that he had simply presented the facts as he had observed them. He added that with the use of protamine zinc insulin, the criteria of good diabetic control must be revamped, since "by the use of this hormone, carbohydrate oxidation is assured for about a twenty-four hour period."

Allen [85] sided with Joslin and his associates in this argument. He reported 2 cases in which disregard of the dietary and insulin control of diabetes over a period of several years greatly increased the require-

83. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: Treatment of Diabetes, J. A. M. A. **115**:1038-1039 (Sept. 21) 1940.

84. Tolstoi, E.: Treatment of Diabetes, J. A. M. A. **115**:1296 (Oct. 12) 1940.

85. Allen, F. M.: Diabetes, J. A. M. A. **115**:1474-1475 (Oct. 26) 1940.

ments of insulin. He concluded that "diabetic patients treated just sufficiently to keep them out of acute trouble for a few years constitute the reservoir from which are drawn the great mass of complications which cause most diabetic deaths today."

It will be many years before Tolstoi and his associates will have the opportunity of properly evaluating their observations, since it will require a long period to determine the incidence of such complications as diabetic retinitis and neuritis among patients treated according to their methods. In the meantime, it will undoubtedly be preferable to leave the study of such methods of treating diabetes to well organized groups like Tolstoi's rather than to introduce such revolutionary concepts into the care of diabetic patients by the average physician.

More recently, various other types of insulin have been reported which provide the type of control of diabetes that every one is seeking. In several reports the use of hexamine insulin (a compound of insulin and hexamethylene tetramine) was advocated.[86] Alpert [86a] reported the cases of 2 boys, one 9 and the other 16 years of age, who received single injections of a mixture of protamine zinc insulin and hexamine insulin before breakfast, with good results. He expressed the opinion that, although mixed, the two insulins retained their individual characteristics, the hexamine insulin producing an immediate and intermediate action and the protamine zinc insulin a delayed action. Feinblatt and his associates [86b] reported that a single dose of the hexamethylene tetramine-insulin compound gave both a rapid and a sustained action. They reported that a single dose of this new insulin produced a blood sugar curve similar to the one produced by four divided doses of standard insulin, but with decided constriction in the range of fluctuations of the levels of blood sugar. The hypoglycemic shock experienced with this preparation was comparable to that which may follow the use of regular insulin and responded promptly to the ingestion of carbohydrates.

Insulin Shock Therapy.—Tremendous doses of insulin have been utilized extensively within the last few years for the induction of shock in the treatment of various conditions. Jourdonais and Bruger [87] studied the sojourn of insulin in the blood of rabbits after the administration of

86. (*a*) Alpert, B.: Juvenile Diabetes Mellitus Treated with Protamine-Hexamine Insulin—a New Combination: Clinical Case Reports, Arch. Pediat. **56**:647-649 (Oct.) 1939. (*b*) Feinblatt, H. M.; Ferguson, E. A., and Alpert, B.: Hexamine Insulin: Juvenile Type of Diabetes Treated with Hexamethylene Tetramine Insulin Compound Giving Rapid and Sustained Action, Endocrinology **26**:437-443 (March) 1940.

87. Jourdonais, L. F., and Bruger, M.: The Sojourn of Insulin in the Blood of Rabbits After the Administration of Massive Doses of Insulin, Endocrinology **26**:250-254 (Feb.) 1940.

massive doses of insulin. They injected 1,000 units of insulin into rabbits and studied the amount of insulin in the blood stream for sixty to ninety minutes after injection. More than ninety minutes after injection, insulin could not be recovered from the blood by the procedure which they employed, although the effect of the insulin, as measured by the hypoglycemia, persisted for as long as nine hours. It is interesting to note that in 2 animals this massive dose of insulin was followed by a gradual and persistent rise of the level of blood sugar; the usual hypoglycemic effect of insulin was not evident. In spite of extremely high levels of the blood sugar, these animals died in convulsive seizures not unlike those seen in insulin shock. Five rabbits in this series showed only transient hypoglycemia, lasting approximately an hour. The authors stated that massive doses of insulin may so disturb the carbohydrate metabolism as to result in ketosis.

Appel and Hughes [88] studied schizophrenic patients who were receiving tremendous doses of insulin for shock therapy. They found that if insulin was given for as long as two months in daily doses large enough to produce coma in patients whose carbohydrate metabolism was normal, an elevation of the dextrose tolerance curves would also be produced. This effect disappeared in two to three months after cessation of therapy. Kaplan and Low [89] studied both dextrose and insulin tolerance tests in relation to insulin shock treatment. Although the average blood sugar curve of 26 patients who had received such treatment and who were subsequently given a dextrose tolerance test was within normal limits, in only 6 cases were the individual curves normal. The blood sugar curves obtained in the insulin tolerance tests of these 26 patients were characterized by a marked prolongation of the time required for a return to the fasting level of blood sugar. There was no correlation between the results of the insulin therapy and the dextrose tolerance tests and the average dose required to produce coma. The onset of coma seemed dependent not only on a significant decrease in the level of blood sugar but on the length of time the low level was maintained.

Sherrill and MacKay [90] studied the effects of tremendous doses of insulin on the rat. They reported that the administration of dextrose was without influence if the duration of the convulsion was long. Insulin-treated rats died of respiratory failure and at necropsy were

88. Appel, J. W., and Hughes, J.: The Effect of Large Doses of Insulin on Glucose Tolerance, Am. J. M. Sc. **199**:829-833 (June) 1940.

89. Kaplan, M., and Low, A. A.: Glucose and Insulin Tolerance: Relation to Insulin Shock Treatment, Am. J. Psychiat. **96**:689-697 (Nov.) 1939.

90. Sherrill, J. W., and MacKay, E. M.: Deleterious Effects of Experimental Protamine Insulin Shock, Arch. Int. Med. **64**:907-912 (Nov.) 1939.

found to have definite edema of the lungs. Administration of strong solutions of dextrose by stomach tube or intraperitoneally to rats that had been in insulin shock for some time was often followed by convulsions and death. Occasionally, water had the same effect. These results were due to the sudden shift in electrolytes and changes in the concentration of body fluids superimposed on an impaired general circulation and cerebral stasis and to degenerative changes, especially in the brain, caused by hypoglycemia. They felt that prolonged hypoglycemia caused permanent functional damage to the brain. After five or six days they noted sensory and motor disturbances, such as impaired vision and hearing, incoordination, spasticity and paralysis.

Results of such studies on rats may explain some of the unfortunate conditions which have been seen among diabetic patients after severe reactions to insulin. Frostig [91] reported clinical observations of 6,587 treatments of schizophrenia with insulin. He found that at first the cerebral cortex became suppressed and released the syndromes associated with activity of the basal ganglions. Activity of the basal ganglions later ceased and gave way to release of the midbrain. Finally, centers in the medulla were released. If signs of medullary release lasted beyond the time at which pinpoint pupils were observed and the corneal reflex disappeared, protracted shock resulted. This point was considered by the author to be the biologic borderline, beyond which treatment could not be continued safely. Sonenthal and Low [92] studied the electrographic tracings of patients after combined shock therapy with insulin and metrazol. They found no evidence of myocardial damage in 36 cases studied after termination of the entire course of treatment with both metrazol and insulin.

Miscellaneous.—The question as to whether antibodies may develop after the use of insulin has been discussed for some time. Wasserman and his associates [93] studied the antigenic property of insulin. They stated that insulin could be considered antigenic because serums from insulin-sensitized rabbits may give a positive reaction in the complement fixation test. Sufficient foreign protein evidently was present in commercially prepared insulin to allow sensitization of a rabbit to that protein by repeated injection of the insulin. Antibodies produced against insulin were not found to act as antihormones. Marble and his

91. Frostig, J. P.: Clinical Observations in the Insulin Treatment of Schizophrenia: Preliminary Report; I. The Symptomatology and Therapeutic Factors in the Insulin Effect, Am. J. Psychiat. **96**:1167-1190 (March) 1940.

92. Sonenthal, I. R., and Low, A. A.: Electrocardiographic Studies After Treatment with Insulin and Metrazol Shock, J. Nerv. & Ment. Dis. **91**:423-427 (April) 1940.

93. Wasserman, P.; Broh-Kahn, R. H., and Mirsky, I. A.: The Antigenic Property of Insulin, J. Immunol. **38**:213-219 (March) 1940.

co-workers [94] studied the effect of plasma from diabetic patients on the blood sugar curves of rabbits following the injection of insulin. Their method was similar to that described by Dohan.[95] They reported the effect of a single subcutaneous injection of approximately 10 cc. of blood plasma from diabetic patients on the hypoglycemic effect of insulin on rabbits. With two exceptions, no significant alterations in the rabbits' blood sugar curves were found even when plasma from obese middle-aged or elderly women who had mild diabetes was used. The series of patients from whom samples of blood plasma were obtained also included 5 who had high requirements for insulin. When the plasma of 2 of these 5 patients was used, a definite lessening of the hypoglycemic effect of insulin subsequently injected into the rabbits was present and persisted for three to five weeks. The results could not be duplicated, however, with serum collected from the same 2 patients at a later date.

HYPERINSULINISM

During 1940 there were two advances in our knowledge of hyperinsulinism. The first was the report of additional proved cases of this interesting condition; the second was the increasing insistence that the term hyperinsulinism be reserved for those cases in which there is proof that the symptoms are caused by the excessive production of endogenous insulin.

True hyperinsulinism is a rare disease. Frantz,[96] who recently reviewed the world literature, found only 96 cases in which the diagnosis had been proved at operation or necropsy. Hypoglycemia, on the other hand, is much more common and may be present physiologically or may be due to any one of many disturbances in carbohydrate metabolism. Meakins [97] reported 3 cases of postencephalitic Parkinson's disease in which attacks of convulsions were associated with low values of blood sugar. He urged further search for other cases in which a connection between a hypothalamic lesion and hypoglycemia was suggested. Adlersberg and Friedman,[98] who reported on disturbances of carbohydrate metabolism in 21 cases of postencephalitic Parkinson's disease, observed pathologically low levels of blood sugar in only 3 cases; these

94. Marble, A.; Fernald, A. T., and Smith, R. M.: Effect of Human Diabetic Plasma upon Blood Sugar Curves in Rabbits Following Insulin, Endocrinology **26**:735-742 (May) 1940.

95. Dohan, F. C.: Analysis of Insulin Response of Rabbits After Injection of Diabetic Serum, Proc. Soc. Exper. Biol. & Med. **39**:24-28 (Oct.) 1938.

96. Frantz, V. K.: Tumors of Islet Cells with Hyperinsulinism: Benign, Malignant and Questionable, Ann. Surg. **112**:161-176 (Aug.) 1940.

97. Meakins, J. C.: Hypoglycemia Following Encephalitis, Ann. Int. Med. **13**: 1830-1836 (April) 1940.

98. Adlersberg, D., and Friedman, R., cited by Meakins.[97]

levels were observed after oral administration of 50 Gm. of dextrose. Hypoglycemia was reported by Rathery, Dérot and Sterne [99] in 2 cases of subdural hemorrhage and by Birnbaum and Wood [100] in cases of dementia paralytica.

Hyperglycemia may be present in many instances without associated organic disease. Matthews [101] determined the postabsorptive values of blood sugar of 117 normal persons and found that they varied from 0.06 to 0.11 Gm. per hundred cubic centimeters of whole blood; the values of 70 per cent fell between 0.07 and 0.08 Gm. Hart and Lisa [102] analyzed all determinations of blood sugar, including routine determinations in 21,000 cases, made over a six year period at the New York City Hospital. In about 11 per cent of cases the concentration of blood sugar was less than 0.08 Gm. per hundred cubic centimeters of whole blood, in 7 per cent between 0.070 and 0.079 Gm., in 2.3 per cent between 0.060 and 0.069 Gm., in 0.8 per cent between 0.050 and 0.059 Gm. and in 0.4 per cent less than 0.050 Gm. Symptoms were not noted in any case, with the exception of 1 in which the level of blood sugar was 0.030 Gm. per hundred cubic centimeters.

Sufficiently strenuous exercise may produce severe hypoglycemia even among trained and healthy athletes.[103] Patients who are nervous or high-strung seem less able than others to withstand effectively the strain placed on the homeostasis of the blood sugar by exercise. Michael [104] performed several determinations of the blood sugar on each of 30 golfers while they were playing eighteen holes of golf after eating their usual luncheon. The values dropped to hypoglycemic levels (the average value was 0.054 Gm. per hundred cubic centimeters) between the ninth and fifteenth holes, or about two hours after the meal. The

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99. Rathery, F.; Dérot, M., and Sterne, J.: Hypoglycémie dans deux cas d'hémorragie méningée sous-arachnoïdienne, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:1578-1582 (Nov. 2) 1931.

100. Birnbaum, L., and Wood, J. A.: Hypoglycemia as a Cause of Seizures in General Paralysis, M. Bull. Vet. Admin. **14**:236-240 (Jan.) 1938.

101. Matthews, M. W.: A Study of the One Dose Three Hour (Standard) and the Two Dose One Hour (Exton-Rose) Glucose Tolerance Tests, Thesis, University of Minnesota Graduate School, 1939.

102. Hart, J. F., and Lisa, J. R.: The Rate of Occurrence of Hypoglycemia: Study of Twenty-One Thousand Routine Fasting Blood Sugars, Endocrinology **27**:19-22 (July) 1940.

103. Levine, S. A.; Gordon, B., and Derick, C. L.: Some Changes in the Chemical Constituents of the Blood Following a Marathon Race, with Especial Reference to the Development of Hypoglycemia, J. A. M. A. **82**:1778-1779 (May 31) 1924. Jokl, E.: Sportärztliche Kasuistik, Klin. Wchnschr. **12**:913-914 (June 10) 1933.

104. Michael, P.: Blood Sugar Studies on Golfers, J. A. M. A. **115**:286-287 (July 27) 1940.

hypoglycemic period corresponded to a period of fatigue, mild symptoms of hypoglycemia and lessened efficiency, as reflected by poorer scores. Both the hypoglycemia and the severity of symptoms were exaggerated among the poorer golfers, apparently because of tension, anxiety and greater output of energy, and were far less than average among the expert golfers, who were usually well poised and relaxed. A second observation was made on the same golfers after they had eaten food which contained more fat and less carbohydrate; consumption of sugar or candy at the seventh and eighth holes resulted in elimination of both hypoglycemia and its symptoms and achievement of much better scores.

THE PITUITARY GLAND

Some of the literature pertaining to the pituitary gland has been reviewed by one of us (E. H. R.) and Schweiger.[105] Reference will be made again to some of that material, as well as to other articles which deal with the relation of the pituitary gland to certain phases of metabolism. The relation of the gland to metabolism of carbohydrates will be considered first. Marks and Young [106] have published many articles in this field, a few of which will be mentioned.

Young [107] reviewed his concept of the relation of the pituitary gland to metabolism of carbohydrates. He began with Houssay's observations, in 1924, (1) that hypophysectomy increased the sensitivity to insulin in normal animals and decreased the intensity of the diabetes in depancreatized animals, (2) that administration of preparations of the anterior lobe of the pituitary gland to normal or hypophysectomized animals decreased their sensitivity to the hypoglycemic effect of insulin, (3) that administration of similar preparations to hypophysectomized depancreatized animals increased the severity of the diabetes and (4) that administration of suitable anterior pituitary extract to normal animals can induce diabetes. Young also reviewed some of the actions of the extract of the anterior lobe of the pituitary. He discussed the anti-insulin action which causes insensitivity to the subsequent injection of insulin. The so-called glycotropic principle may not itself be

105. Rynearson, E. H., and Schweiger, L. R.: Review of Literature on the Pituitary Body (1938 and 1939), Arch. Int. Med. **66**:226-290 (July) 1940.

106. Marks, H. P., and Young, F. G.: The Hypophysis and Pancreatic Insulin, Lancet **1**:493-497 (March 16) 1940; Observations on the Metabolism of Dogs Made Permanently Diabetic by Treatment with Anterior Pituitary Extract, J. Endocrinol. **1**:470-510 (Dec.) 1939. Young, F. G.: The Relation of the Anterior Pituitary Gland to Carbohydrate Metabolism, Brit. M. J. **2**:393-396 (Aug. 19) 1939; Anterior Pituitary Fractions and Carbohydrate Metabolism; I. The Preparation and Properties of Diabetogenic Extracts, J. Endocrinol. **1**:339-355 (Nov.) 1939.

107. Young, F. G.: The Pituitary Gland and Carbohydrate Metabolism, Endocrinology **26**:345-351 (Feb.) 1940.

diabetogenic; although the injection of such extracts may induce a high degree of insensitivity to insulin, the fasting level of blood sugar may be virtually unchanged. Young is not of the opinion that this substance is identical with prolactin, with the thyrotropic, gonadotropic or ketogenic principle of the anterior lobe or with the melanophore-expanding substance from the pars intermedia. Since the glycotropic principle is not diabetogenic in normal animals, it is not identical with the diabetogenic principle, although it may be a constituent of the diabetogenic complex. This glycotropic principle has not yet been distinguished from a number of other pituitary fractions. He questioned whether there was a separate ketogenic factor or whether this was simply a part of the diabetogenic principle.

Diabetogenic Action of Extracts of the Anterior Lobe of the Pituitary Gland.—The ability of crude extracts of the anterior lobe to induce symptoms of diabetes in normal animals is lost if the glands are allowed to remain at room temperature for some hours prior to extraction; however, administration of the heat-stable substances of the anterior lobe to hypophysectomized depancreatized animals may cause an increase in glycosuria. The diabetogenic principle may be made up of two parts, one of which is heat labile and the other heat stable; the latter has an extrapancreatic action. In dogs in which diabetes was induced by anterior pituitary extract, the rate of secretion of insulin is diminished. This decrease may be due to partial exhaustion of the secretory mechanism of insulin, brought about by maintenance of high levels of blood sugar by extrapancreatic means, or it may be due to the direct effect of the diabetogenic principle of the anterior lobe of the pituitary gland on the islands of Langerhans.

If anterior pituitary extract is given daily to dogs for seven or more days, hyperglycemia and glycosuria do not occur for three to five days. The sensitivity of the animal to the hypoglycemic effect of insulin decreases during this period, even though the level of blood sugar is not much increased. After the latent period, glycosuria, ketonuria, polyuria, polydipsia and hyperlipemia occur and there is an increase in the animal's weight. The normal levels of glycogen in the liver may be maintained during the diabetes. Continued administration of anterior pituitary extract often fails to prevent the level of blood sugar from decreasing to normal and the diabetic condition from disappearing, although the animal remains relatively insensitive to insulin. A second rise in the level of blood sugar may be caused by increasing the amount of extract given, but this effect, too, disappears. However, in some cases the daily injection of extracts of the anterior lobe for long periods may cause a diabetic condition which does not disappear when the injections are discontinued. This happens if the dose is large enough or if the

amount injected daily is increased every few days. The following generalizations can be made in instances of this permanent diabetes: 1. There are no spontaneous remissions, and ketonuria may increase over a period of a year after cessation of the injections. 2. Dogs can survive for long periods without insulin and, with sufficient food, maintain their weight. 3. If insulin is given and then its administration is ceased, the animal may die in a state resembling diabetic coma. 4. Some dogs may require more insulin to control glycosuria than depancreatized dogs do under similar conditions. 5. On a diet of beef suet only, glycosuria and ketonuria are decreased. 6. The islands of Langerhans reveal histologic changes which include hydropic degeneration and hyalinization. Like the glycotropic substance, this diabetogenic principle has not been shown to be identical with prolactin, with the thyrotropic, glycotropic or gonadotropic substances of the anterior lobe or with the melanophore-expanding substance of the pars intermedia; neither has it been distinguished clearly from the ketogenic, glycostatic or adrenotropic substances. Young expressed the opinion that this principle is not the same as Collip's metabolism-stimulating factor.

Young also reviewed certain facts concerning the possibility of pancreatropic action of anterior pituitary extracts. Results of work performed by himself and by others indicate that frequent injections of an extract of the anterior lobe will produce an increase in the size and number of islets in the pancreas. Under the same conditions, the content of insulin in the pancreas of the rat may increase greatly. He felt that these results might explain the refractoriness to the diabetogenic action of extracts of the anterior lobe.

Young commented on whether there is a separate diabetogenic principle and pointed out many similar features between the diabetogenic and the growth principle. He felt that the growth-promoting action of the extracts of the anterior lobe may be due to ability of the pancreas to secrete sufficient insulin to induce retention of nitrogen and to promote oxidation of carbohydrate. If the pancreas is able to do this, as it is in the rat, then the extracts promote growth; if the available insulin is insufficient to prevent breakdown of proteins, then glycosuria and diabetes result. In the dog, the diabetogenic action may disappear if the islet tissue eventually is stimulated (by the pancreatropic effect of the extract) to produce insulin to overcome it.

Jensen and Grattan [108] discussed the identity of the glycotropic or anti-insulin substance of the anterior lobe of the pituitary gland. They concluded that the glycotropic effect of the anterior lobe of the pituitary

108. Jensen, H., and Grattan, J. F.: The Identity of the Glycotropic (Anti-Insulin) Substance of the Anterior Pituitary Gland, Am. J. Physiol. **128**:270-275 (Jan.) 1940.

was produced by the adrenotropic factor. Regardless of the name or nature of this hormone, the fact remains that there is in the anterior lobe a principle which has an effect on the pancreas. This effect has been studied by many authors, a few of whom are listed.[109] Haist, Campbell and Best [110] recently discussed the possibility of preventing diabetes among children who were likely to have it by administration of small doses of insulin, together with a diet low in carbohydrate and protein and high in fat. Results on experimental animals (rats, dogs and cats) indicated that affording the pancreas the benefit of physiologic rest by these means could improve a diabetic condition by reducing the strain on the remaining islet cells and also by permitting restoration to normal function of some of the exhausted islet cells. The authors explained that after partial pancreatectomy or during prolonged administration of anterior pituitary extracts, the islets were subjected to overstrain, and consequently they underwent hydropic degeneration. If insulin was given during this period of overwork, diabetes often was prevented.

Harrison and Long [111] studied the effects of anterior pituitary extract on the fasting rat. The injection of saline extracts of anterior lobes of pituitary glands of cattle into fasting normal or adrenalectomized rats was followed by a diminished excretion of nitrogen in the urine and by ketonuria. At the same time, hypoglycemia and a marked reduction in the nonprotein nitrogen of the blood were also found. Hypoglycemia developed in fasting adrenalectomized rats given large amounts of sodium chloride and sodium bicarbonate intraperitoneally, and the excretion of nitrogen in the urine was less than normal. The association of a decreased excretion of nitrogen and hypoglycemia suggested to the authors that the reduction in blood dextrose might be the result of diminished glyconeogenesis from protein, due to inhibition of protein catabolism. The changes in the blood dextrose of fasting adrenalectomized rats might also be explained on the basis of inadequate glyconeogenesis from protein following the loss of cortical hormone.

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109. Dohan, F. C., and Lukens, F. D. W.: Antihormone Effects in Pancreatic Diabetes, Proc. Soc. Exper. Biol. & Med. **42**:167-171 (Oct.) 1939. Soong, H. Y.: The Assay of the Insulin Content of the Pancreas in Rats Receiving Anterior Pituitary Extract, Chinese J. Physiol. **15**:335-341 (June 30) 1940. Best, C. H.; Campbell, J., and Haist, R. E.: The Effect of Anterior Pituitary Extracts on the Insulin Content of the Pancreas, J. Physiol. **97**:200-206 (Dec. 14) 1939. Richardson, K. C.: Influence of Diabetogenic Anterior Pituitary Extracts on the Islets of Langerhans in Dogs, Proc. Roy. Soc., London, s.B **128**:153-169 (Jan. 4) 1940.

110. Haist, R. E.; Campbell, J., and Best, C. H.: The Prevention of Diabetes, New England J. Med. **223**:607-615 (Oct. 17) 1940.

111. Harrison, H. C., and Long, C. N. H.: Effects of Anterior Pituitary Extracts in the Fasted Rat, Endocrinology **26**:971-978 (June) 1940.

Russell [6] reviewed the relation of the anterior lobe of the pituitary gland and the adrenal cortex to the metabolism of carbohydrate. In summary, she stated that in normal rats fed dextrose both whole anterior pituitary extract and adrenal cortex extract when given in large amounts appeared to depress the utilization of carbohydrates and to promote the deposition of glycogen. The former increased storage of glycogen in muscle only, and the latter more markedly affected the stores of glycogen in the liver. An adrenotropic extract of the anterior lobe of the pituitary, which contained the metabolic factors, also depressed the oxidation of carbohydrates and increased the deposition of glycogen in muscle. In adrenalectomized rats, large amounts of adrenal cortex extract increased the glycogen in the liver at the expense of oxidation but did not affect the glycogen in muscle; however, anterior pituitary extract given in the presence of adrenal cortex extract resulted in the usual action of the extract on oxidation and muscle glycogen, even though the dose of cortical extract itself was too small to be effective. The two extracts apparently had a synergistic and complementary effect on the metabolism of dextrose fed to rats. In fasting rats the anterior pituitary extract maintained levels of glycogen in muscle in the absence of the adrenal cortical extract without affecting the amount of glycogen in the liver or the blood sugar, whereas cortical extract, probably by promoting glyconeogenesis, increased stores of glycogen in the liver and maintained levels of blood sugar, although it did not seem to affect directly the stores of glycogen in muscle.

Flint [112] published some interesting observations on hypophysial diabetes and the action of the so-called Macallum-Laughton synergist. He stated:

> As it stands, diabetes represents a derangement in the normal antagonism and regulation exercised by the anterior pituitary and the pancreaticoduodenal ensemble upon the control and regulation of the sugar exchange as well as the wider field of the intermediate carbohydrate metabolism. This glucopathy is its major characteristic symptom.

He contended that under normal conditions the chief hypoglycemic factor is insulin, which primarily governs the utilization and storage of sugar. The stabilization of the glycemic level through static action and an anchor effect is mediated by the Macallum-Laughton synergist, which normally checks hyperglycemia or hypoglycemia for either a long or a short term and acts synergistically with insulin. Flint considered that its therapeutic action consisted in producing these effects in long symmetric patterns in the blood sugar curve, which might last for months.

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112. Flint, J. M.: Further Observations on Hypophyseal Diabetes and the Action of the Macallum-Laughton Synergist, London, A. B. Macallum, 1939.

Paschkis and Schwoner [113] reported that the feeding of protein was followed by the output in the urine of a factor which when injected into rats produced a decrease of the nonprotein nitrogen constituents of the blood. This reaction may be obtained by injection of an alkaline extract of the anterior lobe of the pituitary gland. These authors expressed the opinion that the factor in the urine originated in the pituitary gland.

Farr and Alpert [114] studied the effects of various endocrine extracts on the amino acids in the blood and reported incidental findings as to the blood sugar and urea. They concluded that intravenous injection of extracts containing the growth and metabolic factors of the anterior lobe of the pituitary, or of pitressin, chorionic gonadotropin (antuitrin S), adrenal cortex extract, testosterone propionate or thyroxin, was followed by marked decreases in the concentration of amino acids in the blood plasma. The intraperitoneal injection of an extract containing the growth factor of the anterior lobe of the pituitary produced a transient fall of the amino acids in the plasma. These findings were not accompanied by significant or consistent changes in the amount of sugar or urea in the blood. Subcutaneous injection of insulin or of epinephrine hydrochloride produced sharp decreases in the plasma amino acids, with a mutually opposite effect on the level of blood sugar. The changes in the plasma amino acids after injection of insulin were not accompanied by a corresponding change in the amount of amino acids in the cells.

Diabetes Insipidus and the Antidiuretic Principle of the Posterior Lobe of the Pituitary Gland.—Fisher [115] reviewed the knowledge of diabetes insipidus and of the neurohormonal control of water balance. Both the hypothalamus and the pituitary gland are concerned in the maintenance of water balance. Diabetes insipidus has a complex etiology. Alterations in both the hypothalamus and the pituitary gland and in the connection between the two, which involves the hypothalamic nuclei with their axons to the neurohypophysis, are the causative factors. Fisher referred to the hypothalamicohypophysial system, which consists of certain hypothalamic nuclei, axons to the neurohypophysis and the neurohypophysis itself, including the median eminence, the infundibular stalk and the infundibular process. As the result of detailed studies, he reported that injury to any part of the hypothalamicohypophysial system was reflected by the presence of degenerative changes in other parts of

113. Paschkis, K. E., and Schwoner, A.: The Output of Protein Metabolism Hormone of the Pituitary Anterior Lobe, Endocrinology **26**:117-122 (Jan.) 1940.

114. Farr, L. E., and Alpert, L. K.: The Effect of Endocrine Extracts on the Amino Acids in the Blood with Incidental Findings on the Blood Sugar and Urea, Am. J. Physiol. **128**:772-781 (March) 1940.

115. Fisher, C.: Diabetes Insipidus and the Neurohormonal Control of Water Balance, Proc. Inst. Med. Chicago **13**:117-119 (May 15) 1940.

the system. Diabetes insipidus is a hormonal disturbance attributable to deficiency in the production of the antidiuretic principle by the neurohypophysis. It is a nervous disturbance so far as lesions of the hypothalamus result in changes in the neurohypophysis. The atrophic neurohypophyses from cats with diabetes insipidus were markedly deficient in antidiuretic, pressor and oxytocic activity. Neurohypophysial extracts are antidiuretic. Initially, polyuria and polydipsia result. Then there is a normal phase, after which diabetes insipidus becomes permanent. Polyuria precedes polydipsia. The anterior lobe (pars distalis) of the pituitary gland exerts a diuretic effect. Thyroidectomy temporarily inhibits diabetes insipidus. Thyroid and sodium chloride have a greater diuretic effect on diabetic than on normal animals. Castration and pregnancy produce little change in diabetes insipidus. The pars nervosa rather than the pars intermedia of the pituitary gland elaborates the active principles of the so-called posterior lobe. The supraopticohypophysial portion of the hypothalamicohypophysial system regulates the secretion of the antidiuretic principle by the neurohypophysis. This principle acts chiefly on the kidney and prevents excretion of excessive amounts of urine. Polyuria is due to diuretic processes in the body unchecked by the antidiuretic mechanism. The diuretic processes are the result of activity of the anterior lobe. This activity is due to general control over metabolism rather than to a specific diuretic hormone. This relation of the pituitary gland and water diuresis has been reviewed in an editorial.[116]

Baker and Craft[117] described the observations at necropsy in the case of a pituitary dwarf, 18 years of age, who had severe and permanent diabetes insipidus and who had been studied for eight years. Bilateral destructive lesions limited almost exclusively to the region occupied by the supraoptic nuclei were found. Most of the destruction was in the lateral walls of the optic recess. The neurohypophysis was replaced completely by hyalinized connective tissue. Kylin[118] reported hypophysial transplantation in a case of diabetes insipidus. The patient was a woman, 22 years of age, who had received an injection of finely divided hypophysial gland into the gluteus muscle. He stated that improvement occurred but did not indicate how long it lasted.

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116. The Pituitary Gland and Water Diuresis, editorial, J. A. M. A. **113**: 2322-2323 (Dec. 23) 1939.

117. Baker, A. B., and Craft, C. B.: Bilateral Localized Lesions in the Hypothalamus with Complete Destruction of the Neurohypophysis in a Pituitary Dwarf with Severe Permanent Diabetes Insipidus, Endocrinology **26**:801-806 (May) 1940.

118. Kylin, E.: Hypophysentransplantation in einem Fall mit Diabetes insipidus, Acta med. Scandinav. **101**:566-567, 1939; abstracted, Endocrinology **26**:933 (May) 1940.

Treatment of Peptic Ulcer with Posterior Pituitary Preparation.—Metz and his associate [119] reported their results in the treatment of peptic ulcer with posterior pituitary preparations. They obtained satisfactory clinical results in 76 cases of peptic ulcer. Intranasal insufflation of posterior pituitary in powdered form proved to be the most satisfactory mode of administration. This reference is included because of the obvious importance of having further work of this type conducted under careful control.

Hypopituitarism and Simmonds' Disease.—Magendantz and Proger [120] discussed the differential diagnosis of anorexia nervosa and hypopituitarism. Many reports of Simmonds' disease, or pituitary cachexia, continue to be recorded in the literature, and many conditions apparently examples of this disease continue to be diagnosed more properly as anorexia nervosa. Simmonds' disease is one of the rarest conditions known; anorexia nervosa is much more common. The fact that these two conditions simulate each other so closely undoubtedly explains the incorrect use of the term Simmonds' disease for the more common condition of anorexia nervosa.

OBESITY

The current literature on obesity is concerned chiefly with the extremely controversial subject of the pathogenesis of this condition. Obesity is considered by different observers to be either exogenous or endogenous. Those who maintain that excessive weight is exogenous, that is, that obesity represents an imbalance between the intake of food and the output of energy, point out that the most effective treatment is ingestion of a diet low in calories and that no endocrine preparations available can by themselves bring about the same therapeutic result. On the other hand, observers who maintain that obesity is the result of endogenous disturbances have presented an imposing array of data to support their contention that disorders of one or several of the factors, endocrine and otherwise, which control fat metabolism are operative in accumulation of excessive body weight. However, supporters of the endogenous theory are not at all in agreement as to the site of disturbance. Some observers deny that the abnormality is localized in the endocrine system, while others attribute to the endocrine system a major role in the pathogenesis of obesity. Furthermore, there is no uniformity of opinion as to the gland, or group of glands, primarily

119. Metz, M. H., and Lackey, R. W.: Peptic Ulcer Treated by Posterior Pituitary Preparations: Clinical and Experimental Observations, Am. J. Digest. Dis. **7**:27-32 (Jan.) 1940.

120. Magendantz, H., and Proger, S.: Anorexia Nervosa or Hypopituitarism? J. A. M. A. **114**:1973-1983 (May 18) 1940.

involved. Several excellent reviews of the etiology of obesity have appeared recently.[121] Space does not permit more than a few citations from these works.

Rony [121a] included in his monograph a report on his own series of obese patients, both juvenile and adult. A search was made for endocrine abnormalities; diagnosis of glandular disorder was based on the history, on observations pertaining to the growth and sexual and mental development of the patient and, finally, on data obtained by such laboratory procedures as determination of the basal metabolic rate, the dextrose tolerance test and roentgenographic study of the sella turcica and the bones of the hands. The juvenile group consisted of 22 boys and 28 girls between the ages of 7 and 16 years whose average weight was 54 per cent above normal. Only 6 of this entire group, as judged by results of the aforementioned examinations, were considered entirely free of endocrine disturbance. In the majority of instances, various combinations of abnormalities were present; in 68 per cent of cases these abnormalities were considered the result of glandular disturbance. The adult group included 192 women and 8 men; the average age was 31 years and the average weight was 66 per cent above normal. Definite endocrine syndromes were found in only 13 cases, and a diagnosis of probable endocrine disturbance was made in 56. In many of these, the exact localization of the glandular disturbance could not be determined. Of the adult patients, 131 were apparently free from endocrine disturbance.

Goldzieher [121b] discussed the role that each of the endocrine glands could play in the pathogenesis of obesity; he concluded that, although hypothyroidism and adrenal insufficiency rarely play a major role in obesity, the gonads may in some instances be held responsible, especially in obesity occurring at the menopause. The anterior lobe of the pituitary gland is of considerable importance in connection with obesity of the girdle type. He further pointed out that in connection with obesity of the so-called pituitary type, retention of salt and water associated with an excessive appetite (possibly caused by hypoglycemia) may add to the excessive weight.

On the other hand, Bauer [122] stated that the etiologic factor in obesity is "in a very small number of cases an endocrine disturbance." Hetherington [123] reported that he injected chromic acid into the

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121. (*a*) Rony, H. R.: Obesity and Leanness, Philadelphia, Lea & Febiger, 1940. (*b*) Goldzieher, M. A.: Obesity, M. Rec. **151**:98-100 (Feb. 7) 1940. (*c*) Freed, S. C.: Modern Concepts of Obesity, Illinois M. J. **77**:282-284 (March) 1940.

122. Bauer, J.: Common Diagnostic and Therapeutic Errors in the Management of Fat Boys, M. Rec. **151**:89-92 (Feb. 7) 1940.

123. Hetherington, A. W.: Obesity in the Rat Following Injection of Chromic Acid into the Hypophysis, Endocrinology **26**:264-268 (Feb.) 1940.

hypophyses of rats in an attempt to check the possibility that some sort of selective deterioration of the hypophysis might be responsible for pathologic adiposity. Few animals so treated disclosed any perceptible degree of excess deposition of fat; necropsy on those animals which did become overweight revealed considerable hypothalamic damage in addition to destruction of the hypophysis. In subsequent experiments in which hypothalamic lesions were made without involving the hypophysis, almost 100 per cent of the animals became obese. Hetherington concluded that perhaps lesions in the hypothalamus or in a hypophysial-hypothalamic pathway may be of importance in the pathogenesis of obesity.

A wide variety of other theories have appeared in the literature and are considered fully in Rony's review. Briefly, obesity is attributed to one of the following conditions: (1) disturbance in the nervous system, including both the cerebrospinal and the autonomic division; (2) disturbance in the intermediary metabolism of both fat and carbohydrate; (3) an inherited "abnormal anlage for obesity" (Bauer),[122] or (4) variation in the tendency of the adipose tissue to accumulate fat (lipophilia). In this last hypothesis it is assumed that the adipose tissue of the obese person differs from that of the normal person in that it has a greater tendency to accumulate fat and a greater resistance to the mobilization of fat. The majority of authors concluded that none of these theories may be applied to all, or even to a large percentage of, obese patients. Whatever the etiologic factor is the greater number of these patients will respond to a restricted diet without the addition of endocrine preparations or roentgen therapy. Sprague and one of us (E. H. R.)[124] recently discussed in detail a restricted diet, consisting of approximately 585 calories a day, which was found to give excellent results among a considerable number of extremely overweight persons. Such a diet must be supplemented with concentrates of vitamins and calcium.

A good deal of discussion also has appeared in the literature in regard to the relation of obesity to glycosuria. Two or three years ago, Newburgh and Conn[125] reported that middle-aged obese people could have glycosuria in the absence of other symptoms of diabetes and that this would disappear with reduction of weight and would not recur even with an increase in consumption of carbohydrate, provided that there was not a concomitant gain in weight. Recently, Embleton[126] reported

124. Rynearson, E. H., and Sprague, A. W.: Obesity, California & West. Med. **53**:158-162 (Oct.) 1940.

125. Newburgh, L. H., and Conn, J. W.: A New Interpretation of Hyperglycemia in Obese Middle-Aged Persons, J. A. M. A. **112**:7-11 (Jan. 7) 1939.

126. Embleton, D.: Glucose-Tolerance Curves in Five Hundred Obese Cases, Brit. M. J. **2**:739-740 (Oct. 8) 1938.

that of 242 obese males 73 per cent had high dextrose tolerance curves, although only a small number had glycosuria. This tendency toward a diabetic type of tolerance curve was much more apparent in males over 35 years old.

Chaikoff and Connor [127] reported that in depancreatized dogs receiving diets high in fat the continued presence of excessively high amounts of fat in the liver for several months stimulated hepatic fibrosis, even to the extent of causing death. Wood and Cash [128] reported that excessive weight may be an important factor in elevation of the systolic blood pressure.

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127. Chaikoff, I. L., and Connor, C. L.: Production of Cirrhosis of the Liver of the Normal Dog by High Fat Diets, Proc. Soc. Exper. Biol. & Med. **43**:638-641 (April) 1940.

128. Wood, J. E., Jr., and Cash, J. R.: Obesity and Hypertension: Clinical and Experimental Observations, Ann. Int. Med. **13**:81-90 (July) 1939.

Correspondence

PINEALECTOMIES ON YOUNG MAMMALS

To the Editor:—My attention has been called to an article by Weinberger and Grant entitled "Precocious Puberty and Tumors of the Hypothalamus," in the April issue of the ARCHIVES, page 762.

In this article the authors have completely misinterpreted and misstated the work by Dr. Martin and me on the experimental removal of the pineal gland in young mammals, a report of which appeared in the January 1940 issue of the *Archives of Neurology and Psychiatry*, page 23, and to which they refer.

Weinberger and Grant state (page 763): "Davis and Martin performed pinealectomies on rats and cats. In the former they saw no evidence of sexual precocity but claimed that they did so in cats. This opinion was based on observations on only 3 cats out of the 14 that survived the operation." As a matter of fact, we stated in our article that our series of cats consisted of 71 animals, of nineteen litters, none of which died from effects of the operation. At the time the article was in press, 14 animals were *then* under observation, but our paper was based on the collected observations on 71 animals, which a careful perusal of the article would have shown. The statement that only 3 cats out of 14 survived and were the basis for the article is, therefore, entirely erroneous. Graphs were shown of changes in 5 animals which were used for illustrative purposes.

Again, Weinberger and Grant state (page 763): "Many workers in addition have performed the same experiments as Davis and Martin, with opposite results." A careful reading of the enormous literature on this subject will show that this, too, is untrue. Animals as high in the mammalian scale as cats have never been operated on before they were mature. Our experiments were the first of the kind on kittens 6 weeks old. Extirpation of the pineal gland by the Horsley-Clark apparatus had never been done before on any animals, regardless of age. In our opinion, removal of the gland by this method obviated any possible damage to neighboring structures; this our photomicrographs clearly show. Consequently, our observations were made on animals with no other lesion than complete removal of the pineal gland.

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Book Reviews

Bacillary and Rickettsial Infections. By William H. Holmes, M.D., Professor of Medicine, Northwestern University Medical School. Price $6. Pp. 676. New York: The Macmillan Company, 1940.

For the student of internal medicine Dr. Holmes has written an avowedly unconventional textbook. Sensitively aware that the present medical curriculum, with its vast offering of clinical and laboratory technics, tends often to produce the mechanic, rather than the cultivated, wise and skilful physician, the author has dealt with certain of the major infectious diseases from the broadest possible point of view. With this attitude in mind one finds it easy to understand the inclusion of the large amount of historical material, which, parenthetically, is well chosen, the many instructive epidemiologic discussions, the outlines of preventive measures and much information concerning etiologic and pathologic aspects of such infections. But, on this account it must not by any means be assumed that clinical aspects are neglected. The problems of diagnosis and treatment of the disease in the individual patient, however, are brought into a just relationship to its natural and written history. In the author's definition of this relationship not only are these immediate concerns of the physicians illuminated in a manner possible in no other way, but the author's primary objective of presenting certain of the fundamental data of internal medicine in a manner to enlarge the vision of the student is not infrequently attained.

The volume is broken up into sections on the following subjects: pasteurelloses, including plague and tularemia; the rickettsial diseases; brucelloses; enteric infections; bacillary intoxications, under which heading diphtheria and diseases caused by the exotoxigenic anaerobes are dealt with; diseases due to the hemophilic bacteria, and mycobacterial diseases, including an extensive account of the essential facts concerning tuberculosis. Finally, there is a chapter on a variety of rare or less important bacillary infections, such as anthrax and glanders.

At first this choice seems rather surprising, since it omits many infections of the greatest significance. It is also a little difficult to perceive why the description of the rickettsial diseases—so similar as regards their etiologic agents to the virus diseases—should have been inserted between the chapters on plague and tularemia and those on the brucella infections.

This quandary is answered in part by the author's implication that a similar book dealing with infections of coccic, spirochetal and protozoal origin will be published subsequently. Possibly the epidemiologic similarities of typhus and such pandemic scourges as plague and cholera form a good reason for such treatment of the rickettsial diseases.

Errors of fact are extremely few, in spite of the many different fields of investigation from which the author has drawn his material. The factual content, moreover, is abundant when one considers the scope and the general purpose of the book. But it represents a bare minimum for the medical student, who would require, in addition, a more conventional textbook of medicine and certainly standard texts on bacteriology and parasitology. The book will increase the technical knowledge of the pathologist, the bacteriologist and the professional student of epidemics, but these specialists will profit in other ways.

Dr. Holmes deserves much praise for the clear and lively manner in which he has presented these descriptions of infectious disease and for his successful attempt to maintain in this mechanistic age the humanistic tradition which has always characterized the great physicians of the past.

A Symposium on the Blood and Blood-Forming Organs. Price, $3.50. Pp. 264, with illustrations. Madison, Wis.: The University of Wisconsin Press, 1939.

The book is a collection of the papers presented at the Institute for Consideration of the Blood and Blood-Forming Organs held at the University of Wisconsin, Sept. 4 to 6, 1939. In keeping with the stated purpose of the institute, basic principles and newer fundamental scientific aspects of hematology are stressed. The authors, fifteen in number, are all reperesentative leaders in their fields.

Watson presents the recent work on the porphyrins, a field which has been neglected because of the technical difficulties involved. Rhoads reports on a study of "all cases of refractory anemia as they were referred to the [Rockefeller] institute." The study is important because of its comprehensiveness and the conclusions. Articles by Heath on anemia caused by iron deficiency, by Minot on anemia of nutritional deficiency and by Diamond on erythroblastic anemia ably cover these subjects.

Meulengracht describes experimental work concerning the fundamental defect in pernicious anemia. Investigative work on hemolytic anemia is presented by Haden; the work on experimental leukemia, by Furth, and the work on bone marrow cultures, by Osgood.

Forkner presents the topics of monocytic leukemia and subleukemic leukemia with perhaps too little consideration of the distinction between the Nägeli and the Schilling type of monocytic leukemia; he may also place too much emphasis on the "supravital" technic and the oxidase or peroxidase reaction.

There are excellent reviews of Hodgkin's disease by Krumbhaar and of infectious mononucleosis by Downey. Reznikoff, in addition to recording the usual information concerning polycythaemia vera, describes his finding in the bone marrow of thickened capillaries and adventitia and subintimal fibrosis of arteries and arterioles.

Doan points out clinical applications of knowledge of the reticuloendothelial system, and Eagle describes the various theories of blood coagulation and the clinical uses of heparin and vitamin K.

As would be expected, much of the material included has been published elsewhere, and in some instances in more detail, but the book serves a definite purpose, since each of the topics has been presented as an entity and has been brought up to date. The inclusion of a satisfactory bibliography with most of the articles augments their value. An index would have been a useful addition but is not essential to this type of book.

Hemorrhagic Diseases. By Kaare K. Nygaard, M.D. Price, $5.50. Pp. 320, with 59 illustrations. St. Louis: C. V. Mosby Company, 1941.

Nygaard has written a splendid monograph on hemorrhagic diseases. The greater part of the book (almost 200 pages) is devoted to results of experimental and laboratory studies, and only the last, or third, section deals with the hemorrhagic diseases from the clinical point of view.

In part I the author discusses the method of determining the coagulability of the blood, elaborates on the photoelectric principle and goes into detail in the succeeding chapters concerning photelography. The coagulability of blood plasma, the interaction of thrombin and fibrinogen and the coagulant effect of thromboplastin are treated in part II.

To the laboratory worker and the hematologist the monograph should be of inestimable value. The material is presented in a clearcut manner and is adequately illustrated with charts, diagrams and tables. In addition, there is an extremely complete review of the literature. Some of the relatively short chapters have as many as 120 references.

The third section of the book contains a mass of data which are and should be of interest to the clinician. However, this section is relatively short (slightly less than 100 pages) and probably would not be of sufficient value to the clinician to

warrant his making regular use of the book. As a matter of fact, it seems to the reviewer that part III might have been omitted, or else enlarged. It is doubtful if it is of any particular use to the hematologist in the laboratory, although the greater part of the book would interest him, and not the clinician.

Felicitations are due the author for his splendid treatise on blood coagulation. The data and facts he gives are based on personal experience and on the work of others. He has gathered together most of the known material germane to the study of the coagulation of the blood and has presented it in an attractive, albeit scientific, manner. The reviewer does wish, however, that Nygaard had not appended the anemic part III.

Cardiologia (Cardiology). By Jorge Meneses Hoyos, professor at the Mexico School of Medicine and head of the Cardiology Department of the Military General Hospital. Pp. 277. Mexico City: Editorial Cultura, 1939.

The author approached the task of writing this book with the main idea of offering medical students a modern textbook and a ready source of information on the most recent advances in the subject of cardiology. The result, however, is also splendidly adapted to the average practitioner who may wish to bring himself up to date.

All the chapters are concise and to the point, summarizing ably the main characteristics of the anatomic, physiologic, physical diagnostic, roentgenologic and electrocardiographic aspects of the problem. The author does not seem to follow any specified classification and is apparently taxed at times to reconcile the English, French and German points of view. He initiates the description of the pathologic manifestations of the heart with rheumatic infection. He next deals with endocarditis and pericarditis, valvular lesions, congenital diseases and cardioaortic syphilis. The chapter on arteriosclerosis is followed by one on myocardial lesions. The section dealing with secondary cardiopathic conditions is brief and interesting, comprising such cardiac disturbances as follow hypertensive, pulmonary, endocrinologic, obese or anemic conditions. A short reference to cardiac neuroses is followed by discussions of disturbances of cardiac rhythm, cardiac insufficiency and angina pectoris and by one final section on peripheral vascular diseases. Considering the vastness of the topic, the author has limited himself with ability, and his students no doubt will be grateful for the clearcut sketches he has presented. Each chapter is followed by a well selected bibliography, serving as a leader for further and deeper study.

Tratado de quimica normal y patologica de la sangre. By L. Corona, Professor of Chemical Physiology, University of Chile. Second edition. Pp. 944, with 155 illustrations. Santiago de Chile: Ercilla, 1940.

The first edition of this handbook appeared in 1937, and now the second edition is forthcoming. Each edition was written for the clinician as well as the laboratory worker and was designed to explain to the former as simply as possible the underlying physiologic basis for the various laboratory tests that can be performed on blood and to describe for the latter reliable methods for carrying through the different procedures.

The volume represents painstaking work. Eleven hundred and eighty references are given, and by glancing through them it is evident that the author has attempted to keep his information as up-to-date as possible. Among new material, vitamin K, Gibson's dye method for determining blood volume and photoelectric colorimetry are discussed; on the other hand, if the number of references to a man's publications mean anything, the pioneer work in chemical biochemistry of North American investigators has received due recognition. Benedict is referred to eight times, Cullen eleven times, Folin twenty-five times, Henderson thirty times and Van Slyke thirty-one times.

A book of this nature written in Spanish is likely to be more popular south of the border than in the north. The ARCHIVES, however, is glad to acknowledge

such a meritorious publication from a friendly neighbor. The text is clearly written. The illustrations and diagrams are excellent. The book as a whole cannot fail to be useful and much studied.

Herzkrankheiten: I. Physiologie, Beurteilung und funktionelle Pathologie des Herzens. By Prof. Dr. Max Hochrein. Price, 11 marks. Pp. 416. Dresden: Theodor Steinkopff, 1941.

In the foreword the author states that he does not hope to present an exhaustive study of heart disease, but attempts merely to outline his own views on this subject.

The first volume, in a series of three, deals with the physiologic, diagnostic and functional pathologic aspects of diseases of the heart. All are discussed in a clear and understanding manner, with a good correlation between theory and practice.

A 34 page bibliography, in which American authors are well represented, concludes the volume.

The two subsequent parts of this work on heart disease are to be entitled "Clinic on Coronary Disease" and "Therapy of Heart Disease."

Biologie der Grosstadt. By B. de Rudder and F. Linke. Price, 8 marks. Pp. 210, with 49 illustrations. Dresden and Leipzig: Theodor Steinkopff, 1940.

This paper-bound volume contains the transactions of the fourth conference held at Frankfort on the Main, Germany, on May 9 and 10, 1940. There are, in all, twenty papers dealing with various changes which would improve general conditions in a large city. Such titles as "Climate and the City," "The Beginning and Growth of a City," "Characteristics of Industrial Towns," "Nutrition of the City Dweller" and "Nutrition and Incidence of Peptic Ulcer" are an index to the wide variety of topics covered.

The book is of interest so far as it gives an insight into the thought on this subject in wartime Germany.

Age Morphology of Primary Tubercles. By Henry Sweaney, M.D. Price, $5. Pp. 265, with 73 plates, 26 charts and 7 tables. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

It is the author's thesis that if one can establish certain characteristics of a tubercle in relation to its age, then one can deduce from the character of the tubercle the age of the infection, with the various clinical and epidemiologic implications. Whether or not this project is actually workable the reader must decide for himself, but in any event the book contains a mass of interesting factual data on the morphologic aspects of tubercles. There are numerous photomicrographs and reproductions of roentgenograms and diagrams, and the general format is of the best.

The Role of the Liver in Surgery. By Frederick Fitzherbert Boyce, M.D. Price, $5. Pp. 365, with 44 illustrations and 25 tables. Springfield, Ill.: Charles C. Thomas, Publisher, 1940.

In this handsomely printed and profusely illustrated monograph the writer has assembled a great deal of material pertaining to the liver of special interest to the surgeon. Liver function tests from the standpoint of preparation for operation, vitamin K, hepatic function in thyroid disease and, above all, the dreaded and mysterious "liver death" occurring after operation are discussed in detail. There is much in this book of interest, even though it is really a collection of loosely related essays, rather than a systematic treatise.